

Formaldehyde

Guideline

Available data on formaldehyde concentrations in drinking water indicate that intake of formaldehyde from this source is well below the level at which adverse health effects may occur. It is therefore not considered necessary to establish a maximum acceptable concentration (MAC) for formaldehyde in drinking water.

Identity, Use and Sources in the Environment

Formaldehyde is a colourless, flammable gas with a pungent, suffocating odour. It is soluble in water, acetone, benzene, diethyl ether, chloroform and ethanol. It is very reactive and condenses with numerous compounds to produce methylol or methylene derivatives.¹ Formaldehyde is also photodegradable.² Formaldehyde has a log K_{ow} of 0.35 and a Henry's law constant of 3.27×10^{-7} atm·m³/mol.³

Formaldehyde is used in the manufacture of plastics and resins, for the production of intermediates and for other miscellaneous uses, such as chelating agents. Formaldehyde-based resins and plastics accounted for over 60% of formaldehyde use in the United States in 1978. Urea-formaldehyde resins (>25% of total formaldehyde-based resins) are used principally as adhesives in the manufacture of particleboard, fibreboard and plywood. Phenolic, melamine and polyacetal formaldehyde-based resins are used as adhesives in plywood, surfacing coatings, molding compounds, thermo-setting resins in laminates and other products, such as plastic plumbing fixtures.^{1,4} Formaldehyde is also used as a disinfectant in many human medicines and cosmetics, as an antiseptic in veterinary drugs and biologicals and in fungicides, textiles and embalming fluids.^{1,5}

Formaldehyde occurs in air as a product of the natural photo-oxidation of atmospheric hydrocarbons emitted in automobile, truck and aircraft exhausts.¹ Automobile exhaust has been reported to account for much of the formaldehyde present in the atmosphere.^{1,6} Combustion processes in power plants, manufacturing facilities, incinerators and petroleum refineries are also sources of formaldehyde emissions.¹

Formaldehyde may be released in indoor air from urea-formaldehyde foam insulation or from particleboard that uses adhesives containing urea-formaldehyde resins.¹ Formaldehyde has been reported in industrial and municipal aqueous effluents resulting from chemical, oil and coal processing, resin production and the manufacture and use of resin glues.¹

Formaldehyde biodegrades rapidly in water, and, since it can be readily degraded by bacteria in the soil, bioaccumulation does not occur.^{1,7}

Exposure

Formaldehyde enters drinking water via industrial effluent, leaching from polyacetal compression fittings in plastic potable water lines^{4,8} and ozonation of humic substances and other organic material.^{9,10} Formaldehyde production in the treatment of surface water appears to be proportional to the total organic carbon content of the raw water,¹⁰ although Huck *et al.*¹¹ did not observe a quantitative relationship between formaldehyde levels and raw water non-volatile organic carbon concentration. In water lines, an interior protective coating generally separates the water from the polyacetal resin. If a break occurs in the coating, however, the water may come in direct contact with the resins, resulting in a continuous release of formaldehyde into the water via hydrolysis of the resin surfaces. The resultant concentrations of formaldehyde vary depending on the residence time of water in the pipes; levels may approximate 20 µg/L in occupied dwellings with normal water usage or reach 100 µg/L in unoccupied dwellings or after a few days of no water usage.⁸

In 16 of 34 U.S. water treatment plants, formaldehyde was detected in the influents at levels ranging from 1.2 to 13 µg/L (median 2.8 µg/L).¹² The median value for all 34 of the plants was <1.0 µg/L.¹² For three plants using ozone, formaldehyde levels in influent ranged from <1.0 to 3.2 µg/L, while concentrations as high as 31 µg/L were detected in the ozonated drinking water.¹² In Edmonton, formaldehyde levels in raw water for the 10-month period from March 1989 to January 1990 averaged 1.2 µg/L and peaked at 9 µg/L. Test ozonation

increased the mean formaldehyde level from 1.2 µg/L to 2.2 or 3.2 µg/L, depending on the ozone dosage.¹¹

Formaldehyde may be present in foods naturally or as a result of contamination.^{1,13} Concentrations of formaldehyde ranging from 3 to 26 mg/kg have been reported in a variety of food materials. Some food additives, such as hexamethylenetetramine, have been reported to decompose gradually to formaldehyde in the presence of proteins or under acidic conditions.¹ Daily intake of formaldehyde from food is difficult to evaluate; however, the World Health Organization (WHO) estimated it to be in the range of 1.5–14 mg/d (mean 7.75 mg/d) for an average adult.⁵ Owen *et al.*⁸ estimated it to be 11 mg/d based on a North American diet.

The general population is exposed to formaldehyde mainly by inhalation. It has been estimated that an individual smoking 20 cigarettes per day would receive from 0.38 to 1.0 mg/d by this route.^{5,6} Formaldehyde is released into the air from resin glues and plastic materials, and low air levels (parts per billion) may result from the photo-oxidation of fossil fuel-derived hydrocarbons. In one study in Atlanta, Georgia, the ambient levels of formaldehyde at four locations between July and August 1992 were reported to average between 2.7 and 3.0 ppb, with a peak level of 8.3 ppb.¹⁴ In the early 1980s, average Canadian formaldehyde levels in homes ranged from 0.014 to 0.042 mg/m³, whereas the average level in homes with urea–formaldehyde foam insulation was 0.066 mg/m³.^{15,16} The overall daily inhalation exposure for an average adult has been approximated as 0.3–2.1 mg (average 1 mg), with exposures as high as 5 mg/d.⁵

Assuming a contribution of approximately 9.4 mg/d from food,^{5,8} 1 mg/d from inhalation⁵ and 0.15 mg/d from water (worst-case scenario: 100 µg/L),⁸ an adult would receive 10.55 mg of formaldehyde per day. Less than 2% of this total intake would, therefore, come from drinking water.

Analytical Methods and Treatment Technology

Formaldehyde in drinking water is generally analysed by high-performance liquid chromatography following derivatization with 2,4-dinitrophenylhydrazine and liquid–solid extraction. The detection limit is 6.2 µg/L.¹⁷ Using liquid chromatography, formaldehyde recovery was shown to exceed 90% for concentrations ranging from 20 to 200 µg/L.⁴

Huck *et al.*¹¹ studied the formation and removal of formaldehyde at various treatment steps in an Edmonton drinking water pilot plant that was testing ozone. There was little removal of formaldehyde as a result of coagulation–flocculation–sedimentation treatment steps, although peak concentrations were reduced occasionally to an appreciable extent. As noted above, the mean

concentration increased in raw water from 1.2 µg/L to 2.2 and 3.2 µg/L following ozonation at 0.5 and 1.0 mg ozone/mg non-volatile organic carbon, respectively. A significant reduction in formaldehyde formation was observed as the water temperature decreased. The subsequent dual-media filtration step decreased formaldehyde levels to between 0.5 and 0.9 µg/L for three of four filters tested. The mean effluent formaldehyde levels following granular activated carbon (GAC) contactors were in the range of 0.3–0.6 µg/L.¹¹ Formaldehyde was reduced to non-detectable levels when passed through a GAC column with a solution of ozonated humic material.⁹

Health Effects

Pharmacokinetics

Formaldehyde is a product of normal metabolism and is essential for the biosynthesis of certain amino acids in humans.¹⁸ The endogenous tissue levels of metabolically produced formaldehyde range from approximately 3 to 12 ng/g of tissue.¹⁹

Exogenous formaldehyde is taken up into the human body via ingestion, inhalation and dermal exposure. Ingested formaldehyde is readily absorbed by the gastrointestinal tract. Inhaled formaldehyde appears to be readily absorbed by the upper respiratory tract but is not distributed throughout the body because of its rapid metabolism. The average concentrations in the blood of humans, rats and monkeys before and immediately after inhalation exposure (humans: 1.9 ppm for 40 minutes; rats: 14.4 ppm for two hours; monkeys: 6 ppm for four weeks) were not significantly different. Formaldehyde blood concentrations in control and exposed rats, monkeys and humans were measured at 2.24/2.25, 2.42/1.84 and 2.61/2.77 µg/g blood, respectively.^{20,21}

In dermal studies, formaldehyde was absorbed less readily in monkeys than in rats or guinea pigs.²² After intraperitoneal administration to rats, formaldehyde appears to distribute primarily to muscle, with lower levels in the intestines, liver and other tissues.²³

Upon absorption, formaldehyde is rapidly changed to formic acid, via the intermediate S-formylglutathione, by formaldehyde dehydrogenase and other enzymes. The conversion of formaldehyde to formate occurs in the erythrocytes and the liver. The formic acid is further oxidized to carbon dioxide and water by the action of formyltetrahydrofolate synthetase, which catalyses the production of formyltetrahydrofolate from formate and tetrahydrofolate. In alternative pathways, the formate may be converted to a soluble sodium salt and excreted in the urine, or it may be metabolically incorporated into the one-carbon pool for use in biosynthesis.^{2,13}

Following intravenous infusion, the biological half-life of formaldehyde in monkey blood is about

1.5 minutes, with a concurrent rise in formic acid levels.²⁴ Exogenous formaldehyde is cleared from human plasma with a biological half-life of 1–1.5 minutes.² In dogs, the conversion of formate to carbon dioxide and water results in a biological half-life for formate of about 80–90 minutes.²⁵ In humans, it has been calculated that the liver converts 22 mg of formaldehyde to carbon dioxide per minute.^{8,26} The oxidation of formic acid to carbon dioxide and water is slower in monkeys than in rats.²⁷

Metabolites in mice and rats are eliminated in the urine, faeces and expired air, with the relative proportion depending on the route of administration.^{28,29} Increased urine concentrations of formic acid in workers occupationally exposed to unspecified concentrations of formaldehyde in air were found in three of six workers (30.0, 50.5 and 173.0 mg/L, respectively) compared with unexposed workers (17 mg/L).³⁰

Effects on Humans

Irritation and sensitization of the skin have been associated with exposure to formaldehyde in water at levels much higher (5–20% formaldehyde by weight in water) than those encountered in drinking water, although there are conflicting study results at lower concentrations.³¹ Irritation of the eyes, nose and throat results from exposure to as little as 0.25 ppm formaldehyde in air chamber studies and to 1 ppm or higher under normal conditions.¹⁹ At concentrations below 1 ppm, irritation is mild, and adaptation occurs in minutes.³² No acute effects have been observed to result from exposure to formaldehyde at 0.030 ppm in air.³³ Exposure to 50 ppm and above may cause severe injury to the respiratory tract, such as pneumonitis and pulmonary oedema.¹ Haemolytic anaemia occurred in patients undergoing dialysis following contamination of the dialysis water with formaldehyde³⁴; sources of the contamination included formaldehyde solutions used to sterilize dialysis filters as well as formaldehyde leaching from water filters containing cotton fibres bonded with melamine resin.^{34,35} Ingestion of formalin (an aqueous solution of formaldehyde) has been reported to cause inflammation of the linings of the mouth, throat and gastrointestinal tract and eventual ulceration and necrosis of the mucous lining of the gastrointestinal tract, eventually causing kidney damage and circulatory collapse leading to death.^{5,8,13} Other effects associated with formalin ingestion include pneumonia, haemorrhagic nephritis and abortion.³⁶

Chronic oral exposure to formaldehyde occurs primarily from the daily ingestion of low levels of formaldehyde in foods. It has been reported that chronic ingestion of formaldehyde at concentrations of 22–200 mg/d for 13 consecutive weeks did not result in toxic effects in humans, but no other details were reported.^{8,37}

The likelihood of adverse health effects following exposure to low-level airborne formaldehyde, as a result of volatilization from contaminated drinking water, was reviewed by Owen *et al.*⁸ For a formaldehyde concentration of 100 ppb in drinking water, the authors suggested that the induced air concentration would not likely exceed 0.1 ppb. Based on an irritation threshold of 250 ppb in chamber studies¹⁹ and the lack of acute effects following exposure to formaldehyde at 30 ppb,³³ acute or chronic toxicity is not likely to result from such low-level exposure.⁸

A large number of epidemiological studies dealing with formaldehyde exposure have been reviewed by the International Agency for Research on Cancer (IARC),³⁸ Higginson *et al.*,³⁹ WHO⁵ and Heck *et al.*⁴⁰ Several of these studies reported on only a small number of cases or did not show excess cancer rates.³⁸ Those cancer types seen in one or more studies included Hodgkin's disease, leukaemia and cancers of the buccal cavity and pharynx, as well as lung, nose, prostate, bladder, brain, colon, skin and kidney cancer. Increased mortality from leukaemia and brain cancer was generally not reported among industrial workers, which suggested to the authors that these cancers may be due to factors other than exposure to formaldehyde.³⁸ A slight increase in the occurrence of lung cancer reported in several studies did not show patterns of increasing risk related to various measures of exposure (i.e., latency, duration, level or cumulative dose) that are normally seen for occupational carcinogens. Evidence was considered strongest for increased incidence of nasal and nasopharyngeal cancers.³⁸

In a more recently published epidemiological review, no deaths from nasal cancer or increased mortality from other cancers were reported in workers at six British chemical or plastics factories where formaldehyde was manufactured or used. The cohort of 7680 men, first employed before January 1, 1965, was classified in terms of exposure to formaldehyde and then followed to the end of 1981.⁴¹ An additional follow-up of these workers to the end of 1989 and an additional 6357 workers, first employed after 1964, showed no cases of nasopharyngeal cancer. A slight increase in mortality from lung cancer, respiratory disease and stomach cancer was found. However, no relationship with estimated cumulative dose or time since first exposure was observed. It was postulated that the increase in lung cancer mortality was consistent with the possible confounding effects of cigarette smoking.⁴² Marsh *et al.*⁴³ also found no association between mortality from lung cancer or nasopharyngeal cancer and long-term exposure to formaldehyde in a cohort of 7359 workers (first employed between 1941 and 1984) at a chemical plant in Connecticut. No information on smoking and other confounding factors was given in these studies.

While there are a large number of epidemiological studies that deal primarily with inhalation and/or dermal exposure, no studies were found that deal primarily with oral exposure.

In one human reproductive epidemiological study, no effects on sperm (numbers, morphology and 2F-body frequency) were reported in 11 autopsied workers occupationally exposed to formaldehyde (time-weighted average concentrations of 0.61–1.32 ppm). Subjects were matched for sex, age and use of alcohol, tobacco and marijuana and sampled three times at two- to three-month intervals.⁴⁴

Effects on Laboratory Animals and *In Vitro* Test Systems

Acute/Subchronic Studies

Oral LD₅₀ values of 800 and 260 mg/kg bw have been reported for rats and guinea pigs, respectively.^{5,45}

In a four-week study, five-week-old Wistar rats (10 per sex per dose) received formaldehyde in drinking water at dose levels of 5, 25 or 125 mg/kg bw per day. A control group (20 per sex) received drinking water *ad libitum*, and a water-restricted group (10 per sex) was given drinking water in a volume equal to that given to the high-dose treatment group. High-dose rats showed reduced food and water intake, histopathological changes in the stomach (e.g., focal hyperkeratosis of the forestomach and slight focal atrophic inflammation in the glandular stomach) and, in males only, lowered total protein and albumin levels in plasma. According to the authors, the degenerative and proliferative gastric changes seen in rats were probably related to the irritating properties of formaldehyde. The no-observed-adverse-effect level (NOAEL) was determined to be 25 mg/kg bw per day.⁴⁶

Oral doses (in drinking water) of 0, 50, 100 or 150 mg/kg bw per day in Sprague-Dawley albino rats (15 per sex per dose) and 0, 50, 75 or 100 mg/kg bw per day in purebred beagle dogs (4 per sex per dose) for 90 days had no effect on absolute or relative organ weights, haematology, clinical chemistry, urinalysis or gross microscopic pathology of treated animals, when compared with untreated controls. Lower body weight gain was observed in both species at the highest dose level (150 mg/kg bw per day in rats and 100 mg/kg bw per day in dogs) and in male rats given 100 mg/kg bw per day. There was a dose-related decrease in water consumption in male (9%, 18% and 31%) and female (13%, 22% and 30%) rats. There were no differences in mean food consumption by rats at any dose level, but dogs had reduced food consumption at all doses. The authors concluded that relatively large amounts of formaldehyde taken orally are well tolerated.⁴⁷

Carcinogenicity/Chronic Studies

In a two-year study, Wistar rats (70 per sex per group) were exposed to formaldehyde in drinking water at mean doses of 0, 1.2, 15 or 82 mg/kg bw per day for males and 0, 1.8, 21 or 109 mg/kg bw per day for females. Rats were sacrificed at weeks 53, 79 and 105, and the histopathology of organs was performed. Adverse effects were observed only in animals receiving the highest dose and included lower food and water intake, lower body weights and pathological changes in the stomach, characterized by thickening of the mucosal wall in the forestomach and glandular stomach. The histopathological changes included papillary epithelial hyperplasia frequently accompanied by hyperkeratosis located on the limiting ridge as well as focal ulceration in the forestomach and hyperplasia with ulceration of the glandular stomach. Relative kidney weights were increased in high-dose females, and an increased incidence of renal papillary necrosis was found in both sexes. There were no adverse effects on survival, haematology or clinical chemistry at any dose. High-dose male and female rats experienced severe damage to the gastric mucosa, but no gastric tumours or tumours at other sites were found. The NOAEL was determined by the authors to be 15 mg/kg bw per day in males and 21 mg/kg bw per day in females.⁴⁸

In a similar study, Wistar rats (20 per sex per group) were administered formaldehyde in their drinking water at concentrations of 0, 0.02, 0.10 or 0.50% (actual doses estimated to be 0, 10, 50 and 300 mg/kg bw per day) for 24 months. Six rats per sex per group were sacrificed at 12 and 18 months. Rats at the highest dose displayed increased mortality (45% of males and 55% of females died at 12 months, and all animals had died by 24 months), retarded growth, decreased food and water intake as well as lowered levels of serum protein and albumin; however, there were no histopathological changes associated with these biochemical changes. At the end of 12 months, rats of both sexes in this group were observed to have gastric erosions, ulcers (forestomach and glandular stomach), squamous cell hyperplasia, hyperkeratosis and basal cell hyperplasia. Two animals (1/6 males and 1/8 females) from the mid-dose group showed forestomach hyperkeratosis at 18 and 24 months, respectively; however, no mucosal lesions of the glandular stomach were seen. There were no significant differences in the incidences of any tumours among groups. The authors considered the “no-observable-effect level” of formaldehyde to be 0.02% in the drinking water (equivalent to a dose of 10 mg/kg bw per day).⁴⁹

Sprague-Dawley rats (50 per sex per group) were exposed to formaldehyde in drinking water for 104 weeks at concentrations of 0, 10, 50, 100, 500, 1000 or 1500 mg/L (equivalent to doses of 0, 1, 5, 10, 50, 100 or 150 mg/kg bw per day). Individual body weight and

water and food consumption were measured. All animals that died were necropsied and examined histopathologically. A dose-dependent increase in the incidence of leukaemia was reported at dose levels of 5 mg/kg bw per day and higher (total combined percentage of male/female leukaemia incidence: 9, 9, 12, 13 and 18, respectively). An increase in the incidence of gastrointestinal neoplasms was not dose-related. Tumours of this kind were considered rare in historical controls and were not detected in concurrent controls. According to the authors,⁷ formaldehyde is a multi-potential experimental carcinogen; however, the study results are equivocal, since there is a lack of statistical analysis of the data and there were no apparent effects on body weight. In addition, the findings of this study are in contrast to the results of similar studies that reported no tumours at doses of 5 mg/kg bw per day or less.

There is some evidence that exposure to formaldehyde by inhalation causes tumours at the contact site in rats by irritation of the nasal epithelium.^{50,51} In one study,⁵¹ Fischer 344 rats and B6C3F₁ mice (119–121 animals per sex per group) were exposed to mean concentrations of 0, 2.0, 5.6 or 14.3 ppm formaldehyde six hours per day, five days per week, for two years. Haematology, serum chemistry, urinalysis and gross pathology were performed at 6, 12, 18, 24, 27 and 30 months. Squamous cell carcinomas were observed in the nasal cavities of 103 rats (52/120 females and 51/120 males) and two male mice exposed at 14.3 ppm and of two rats (1 per sex) exposed at 5.6 ppm. Histopathology of all tissues revealed compound-related lesions in the nasal cavity only. No tumours were reported in animals exposed at 2.0 ppm.⁵¹ The results suggest a non-linear carcinogenic response (or threshold for carcinogenicity) to inhaled formaldehyde in rats,^{8,52} since a 50-fold increase in tumour incidence resulted from a three-fold increase in the formaldehyde concentration in air.⁵¹ Additional evidence of a non-linear response to formaldehyde is provided by Swenberg *et al.*⁵³ A 10- to 20-fold increase in cell replication was observed in rats and mice exposed to 6 or 15 ppm and 15 ppm, respectively. Exposures of rats to ≤ 2 ppm and mice to ≤ 6 ppm resulted in no increase in cell proliferation. By exposing rats to the same overall daily dose of formaldehyde but varying the concentration and exposure duration, Swenberg *et al.*⁵³ also showed that the tissue concentration of formaldehyde was of greater importance than total cumulative dose in producing a response.

Formaldehyde is highly water soluble and extremely reactive. Since the mucous layer covering the respiratory epithelium of rats is approximately 95% water,⁵⁴ formaldehyde inhaled nasally dissolves readily in the mucous membrane, and the effects of formaldehyde are conveyed to the underlying respiratory epithelium.⁸ While it is possible that tumours at a remote site could be the

result of absorption and distribution of formaldehyde via the circulatory system,⁸ Heck *et al.*⁴⁰ noted that exposure to formaldehyde by inhalation had no measurable effect on the formaldehyde concentration in the blood of rats, monkeys and humans.

Increased cell proliferation is an important marker in formaldehyde carcinogenesis.^{55,56} Compensatory cellular proliferation is a prominent response to cytotoxicity.⁵³ Therefore, carcinogenicity in animals appears to be caused at cytotoxic doses of inhaled formaldehyde.

Based on the available biological data, it can be concluded that chronic exposure of humans to low doses of formaldehyde in drinking water (by ingestion and inhalation) is unlikely to represent a significant hazard, for the following reasons: (1) the delivered dose to the target nasal tissues is less for humans than for obligate nose-breathing rodents, at equal exposures; (2) if formaldehyde in air posed a carcinogenic risk to humans, there should be epidemiological evidence supporting a relationship between exposure and nasal or lung cancer; (3) the intake dose (via ingestion or inhalation) is unlikely to be high enough to overwhelm the process of metabolic detoxification and induce compensatory cellular proliferation in response to cytotoxicity; and (4) the tissue concentration, not the cumulative dose, is the primary determinant of formaldehyde toxicity.⁸

Mutagenicity

Extensive data on the mutagenicity of formaldehyde have been reviewed by IARC³⁸ and WHO.⁵ Formaldehyde is considered to be a weak mutagen. It is mutagenic in prokaryotic and eukaryotic cells *in vitro* as well as *in vivo* in *Drosophila melanogaster* (depending on the route of administration), especially at high concentrations. Addition of S9 metabolizing fractions to the assay systems reduces the mutagenic activity of the chemical.⁵ Inconsistent results were found in *in vitro* mammalian assays, with increases in mutation frequency reported in mouse lymphoma assays, but not in Chinese hamster ovary cells.⁵

Formaldehyde reacts readily with macromolecules in cells, primarily at the point of exposure. It induced chromosomal aberrations and sister chromatid exchanges in a number of cell lines.⁵ However, there was no significant sister chromatid exchange in a human lymphocyte culture below an apparent “threshold” of 5 $\mu\text{g/mL}$ of culture medium.⁵⁷ Craft *et al.*⁵⁸ exposed human lymphoblasts *in vitro* to various concentrations of formaldehyde (0–150 $\mu\text{mol/L}$ for two hours) and indicated that both the induction of mutations and the formation of DNA–protein cross-links by formaldehyde are non-linear functions occurring at overlapping concentration ranges.

In vivo experiments to induce genotoxic effects in rodents exposed to formaldehyde have generally been unsuccessful.^{5,59} Tests for the induction of sister

chromatid exchanges in mouse bone marrow cells gave equivocal results. Dominant lethal tests in ICR-HA Swiss mice were reported to be negative at intraperitoneal doses up to 40 mg/kg bw.⁶⁰ Studies on Q-strain mice showed no effects, except during the first and third weeks, after intraperitoneal treatment of males with formaldehyde at 50 mg/kg bw.⁶¹

Micronucleus and chromosomal assays failed to reveal any formaldehyde-induced lesions in exposed rats and mice.⁵ The results of a somatic cell mutation assay in the C57B1/6J⁴“HA” mouse were also negative for formaldehyde.⁶² In one experiment, formaldehyde increased the number of micronuclei and nuclear anomalies in epithelial cells in rats.⁶³ In humans, no cytogenetic alterations (e.g., chromosomal aberrations or sister chromatid exchanges) were reported in peripheral lymphocytes.^{44,64}

Reproductive/Teratogenicity Studies

No increase in abnormalities in sperm morphology was detected in B6C3F₁ mice following five daily oral doses of formalin (37% formaldehyde, 10% methanol in water) at 100 mg/kg bw.⁴⁴ In a screening study, male rats dosed once orally with a 4% w/v formaldehyde solution at 100 or 200 mg/kg bw displayed a significantly increased incidence of sperm abnormalities (elongated and tapering heads) at the high dose.⁶⁵

Intraperitoneal administration of formaldehyde at doses of 8 or 16 mg/kg bw daily for 10 days caused a significant decrease in absolute and relative weights of male reproductive organs (degeneration of testicular tissues and inhibition of spermatogenesis) without causing any significant change in body weight.⁶⁶

No teratogenic effects were reported in fetuses of pregnant albino mice (34 per group) given formaldehyde by gavage at doses of 0, 74, 148 or 185 mg/kg bw per day on days 6–15 of gestation, even though the highest dose was toxic to the dams.⁶⁷ Growth and viability of neonates from mice given oral doses of 540 mg/kg bw per day on days 8–12 of gestation were not significantly affected.⁶⁸ No effects on pregnancy rate, weight gain of pregnant females, length of gestation, size of litters or health of the offspring (under observation for up to two years) were observed in beagle dogs (9–11 per group) fed formaldehyde at 0, 3.1 or 9.4 mg/kg bw per day in their diet on days 4–56 after mating.⁶⁹

Classification and Assessment

Formaldehyde is a normal product of metabolism and is essential in the biosynthesis of certain amino acids. Rats exposed to formaldehyde by inhalation exhibited an increased incidence of carcinomas of the nasal cavity at doses that caused irritation of the nasal epithelium. Concentrations that are carcinogenic are also cytotoxic and increase cell proliferation in the nose.

However, the weight of evidence indicates that formaldehyde is not carcinogenic by the oral route. Ingestion of formaldehyde in drinking water for two years caused only stomach irritation in rats in several studies, particularly at higher doses.

The tolerable daily intake (TDI) of formaldehyde can be derived by dividing a NOAEL in an animal study⁴⁸ by an appropriate uncertainty factor. For formaldehyde, the TDI is derived as follows:

$$\text{TDI} = \frac{15 \text{ mg/kg bw per day}}{100} = 0.15 \text{ mg/kg bw per day}$$

where:

- 15 mg/kg bw per day is the NOAEL for various effects in male rats, including pathological changes in the stomach and an increased incidence of renal papillary necrosis, in a study in which rats were exposed to formaldehyde in drinking water for two years⁴⁸
- 100 is the uncertainty factor (×10 for intraspecies variation; ×10 for interspecies variation).

Since formaldehyde is metabolized quickly in the body and induces tumours only in animals exposed by inhalation at high cytotoxic doses, and as there is no clear evidence of carcinogenicity by the oral route, an extra uncertainty factor was not used.

Rationale

A guideline value for formaldehyde in drinking water, based solely on health considerations, can be derived from the TDI as follows:

$$\frac{0.15 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.05}{1.5 \text{ L/d}} = 0.35 \text{ mg/L}$$

where:

- 0.15 mg/kg bw per day is the TDI, as derived above
- 70 kg is the average body weight of an adult
- 0.05 is the proportion of total daily intake allocated to drinking water (as most of the exposure to formaldehyde is from food [89%, as calculated from data in the “Exposure” section] and less than 2% is from water, an allocation of 5% of the TDI to drinking water is considered appropriate)
- 1.5 L/d is the average daily consumption of drinking water for an adult.

A health-based guideline value of 0.35 mg/L (350 µg/L) for formaldehyde in drinking water can thus be derived. However, because this concentration is more than 25-fold higher than concentrations normally found in water supplies (1.2–13 µg/L), it is not considered necessary to establish a maximum acceptable concentration (MAC) for formaldehyde in drinking water.

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