DRAFT

INFORMAL GUIDANCE LEVEL FOR FORMALDEHYDE
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Background

The Office of Drinking Water provides advice on health effects upon request, concerning unregulated contaminants found in drinking water supplies. This information suggests the level of a contaminant in drinking water at which adverse health effects would not be anticipated. A margin of safety is factored in so as to protect the most sensitive members of the general population. This guidance is not a legally enforceable standard.

General Information and Properties

Formaldehyde is characterized by the following properties: colorless gas; molecular weight 30, melting point -92° C; boiling point -19° C; vapor pressure -88 at 10 mm Hg; specific gravity 0.815 at 4° C. In aqueous solution, formaldehyde undergoes hydration to yield the monohydrate and polymeric hydrates. The distribution of formaldehyde, as the monomer and polymer, is dependent on the concentration, age, and temperature of the formaldehyde solution (Verschueren, 1977).

The odor threshold of formaldehyde in water has been reported to be 20 mg/liter (Nazarenko, 1960) or 49.9 mg/liter (Baker, 1963).

The American Conference of Governmental Industrial Hygienists (ACGIH, 1974) recommends a threshold limit value (TLV) for formaldehyde of 2 ppm. The present Occupational Safety and Health Administration (OSHA) federal workplace standard for formaldehyde is 3 ppm, as a time-weighted average concentration over an 8-hour workshift (1979).

The stability of formaldehyde in distilled water, tap water, and tap water spiked with soil extract is summarized in a Russian article focusing on allowable concentrations of formaldehyde in water basins (Nazarenko, 1960). The stability of formaldehyde in various water samples was assessed by measuring formaldehyde concentration on days 1, 2, 3, 4 and 5, respectively. The formaldehyde concentrations in various water samples were as follows:

Formaldehyde (mgl) in Water

Experimental Conditions	Original	Determination Time: First Day	Second Day	Third Day	Fourth Day	Fifth Day
Distilled Water	4.5	4.5	4.5	4.5	4.5	4.4
Tap Water	5.0	4.7	4.5	4.0	3.5	2.7
Tap Water + 1 mg/l soil extract	5.0	4.5	4.3	3.7	3.0	1.5
Tap Water + 5 mg/l soil extract	5.0	4.3	3.0	NONE	-	-

The above data show that the formaldehyde concentrations in distilled water remained constant for 5 days and that the rate of formaldehyde concentration abatement in water was highly dependent upon the presence of the relative concentration of microorganisms.

Pharmacokinetics

Formaldehyde enters the body via ingestion, inhalation, dermal absorption or ocular contact. The metabolic fate of formaldehyde has been studies in dogs following oral or intravenous administration of formaldehyde (Malorny et al. 1965). In one phase of the study, dogs were administered at 0.6 percent formaldehyde solution orally by intubation (70 mg/kg body weight). The principal metabolite, formic acid, was detected in the plasma at a level of 7.1 mg percent 20 minutes after dosing and a level of 12.9 mg percent 2 hours after dosing. However, formaldehyde was not detected in the plasma. In another set of experiments, dogs were administered a 0.2M formaldehyde solution intravenously (35 mg/kg body weight). During infusion, the level of formaldehyde in the plasma was 0.95 mg percent while in red blood cells, the level was 4.06 mg percent. One hour following infusion, formaldehyde was no longer detectable in plasma although trace levels were found in erythroctyes (0.2 mg percent). The maximum concentration of formic acid in plasma was 14.4 mg percent after 1 hour, suggesting a rapid transformation of formaldehyde to formic acid. Furthermore, the investigators stated that the biological half-life for formic acid was 90 minutes.

The metabolic fate of ^{14}C-formaldehyde in rats has been studied following intraperitoneal administration (Neely, 1964). Adult female rats were given approximately 70 mg/kg of ^{14}C-

formaldehyde. The investigator reported the following findings: (a) 82 percent of the formaldehyde dose was detected in the expired air as $^{14}CO_2$; (b) urine contained about 14 percent of the isotope in the form of methionine, serine, and an adduct formed from cysteine and formaldehyde, accounting for 96 percent in 48 hours.

The animal studies in rats by Neely (1964) suggest that the absorption of formaldehyde is approximately 100 percent of the formaldehyde dose when administered intraperitoneally. Therefore, in the development of the guidance level for formaldehyde, it will be assumed that 100 percent of formaldehyde will be absorbed by the exposed individual.

Summary of Toxicity Information

The acute toxicity of formaldehyde from different exposure routes has been determined for the following mammalian species:

- Rats, oral LD_{50} = 800 mg/kg; subcutaneous LD_{50} = 400 mg/kg; inhalation LD_{50} = 1 mg/liter (1.0 mg/m^3) (Smyth et al. 1941; Skog, 1950).
- Guinea Pigs, oral LD_{50} = 260 mg/kg (Smyth et al. 1941).
- Mice, subcutaneous LD_{50} = 300 mg/kg (Skog, 1950).

Although a large body of information on the toxic effects in humans and animals from the inhalation of formaldehyde exists, the information concerning effects from oral administration of formaldehyde is very limited.

A study of possible toxic effects of prolonged formaldehyde ingestion was reported by Yonkman et al. (1941). Two human subjects were placed on a daily consumption of "pure" formaldehyde in water for 13 weeks. The subjects initially received 22 mg of formaldehyde per day for the first 14 days. Thereafter the daily dosage of formaldehyde was increased every 7 or 14 days until dosage had reached 200 mg per day by the 13th (final) week. Blood samples were analyzed periodically for hemoglobin content, red or white cell counts and morphology. Urine samples were analyzed for the presence of formaldehyde and albumin. There were no changes in hemoglobin, in the number of red and white blood cells or in cell morphology. Urine analyses were negative for free formaldehyde and albumin. However, the subjects experienced mild pharyngeal and gastric discomfort, but this was alleviated when the formaldehyde dosage was diluted in water by twice the initial concentration.

The results of other formaldehyde ingestion studies in animals were summarized in a Russian review article on allowable concentrations of formaldehyde in water basins (Nazarenko, 1960). Dogs and rabbits were administered formaldehyde diluted in water and milk at daily doses of 2-100 mg/kg for up to 129 days. Deaths were reported in dogs given as little as 2 mg/kg for 50 days. Rabbits were less sensitive; only one died that received 50-100 mg/kg. No effects were observed on hematology, weight gain, or fertility in rats administered formaldehyde by stomach tube at 6-8 mg/kg for 124 days. In another experiment, only slight, inconsistent effects on conditioned reflexes were observed in rats given formaldehyde in the drinking water at 0.5-20 mg/l for 71-118 days. Formaldehyde administered to rats in the drinking water at 1, 5, and 20 mg/l for 11 weeks caused no histologic changes. However, when the dose was increased to 100 mg/l for an additional unspecified period, there were histologic changes in the liver and spleen.

Carcinogenicity

Some experimental data are available which implicate formaldehyde as a potential carcinogen. Horton et al. (1963) exposed mice via inhalation to formaldehyde vapor at concentration of 50, 100, and 200 mg/m^3 for 1 hour three times a week for up to 35 weeks. Formaldehyde exposure was continued after the 35th week for the 50 mg/m^3 group at a level of 150 mg/m^3 for an additional 29 weeks. Histopathologic analysis of the animals exposed to formaldehyde levels of 50 or 100 mg/m^3 revealed basal cell hyperplasia and stratification of the epithelium of the trachea and bronchi at exposure levels of 100 mg/m^3, squamous cell metaplasia was evident. However, there was no evidence of pulmonary neoplasms in mice exposed to formaldehyde vapor at concentration of 50 mg/m^3 for 35 weeks followed by exposure to 150 mg/m^3 for 29 weeks. Ionescu et al. (1978) detected bronchial cell hyperplasia and squamous cell metaplasia in rabbits exposed to formaldehyde vapor (3 percent; 10 g/m^3) for 3 hours daily for up to 50 days. No squamous cell carcinomas were noted.

In contrast, Swenberg et al. (1980) reported the occurrence of squamous cell carcinomas of the rat nasal cavity after inhalation exposure to formaldehyde. In the above study, Fischer rats were exposed via inhalation to formaldehyde vapor at concentrations of 2.5 mg/m^3 (2 ppm), 7.5 mg/m^3 (6 ppm) or 18.7 mg/m^3 (15 ppm), 6 hours/day, 5 days/week, for 18 months of a 24-month study. Histologic examination of the rats revealed a high incidence (18 percent) of neoplasms of the nasal cavities in animals from the 15 ppm exposure group killed at 18 months. Histologic examination of tissues from rats exposed to 15 ppm killed after 6 and 12 months of exposure indicated that formaldehyde-induced lesions (epithelial dysplasia,

squamous metaplasia) were limited to the nasal cavities. Epithelial dysplasia and squamous metaplasia also occurred in animals from the 2, and 6-ppm exposure groups; however, no squamous cell carcinomas were observed.

Mutagenicity

Formaldehyde produces genetic damage in several microorganisms such as Escherichia coli, Salmonella typhimurium, and Saccharomyces cerevisiae. Formaldehyde is weakly mutagenic as observed in bacterial tests: S. typhimurium (Sasaki and Endo, 1978) and E. coli (Nishioka, 1973). Formaldehyde is known to induce DNA-protein cross-links in bacteria (E. coli) (Wilkins and Macleod, 1976) and in yeast (S. cerevisiae) (Magana-Schwencke and Ekert, 1978). Formaldehyde-induced mitotic recombination has also been reported (Chanet et al. 1975).

Reproductive and Teratogenic Effects

Based on the currently available data from animal studies, formaldehyde does not appear to have an adverse effect on reproductive processes, embryonic and fetal development, or organogenesis. Hurni and Ohder (1973) reported no adverse reproductive effects in beagle dogs exposed to formaldehyde. In the above study, dogs were fed diets containing 125 ppm (3.1 mg/kg/day) or 375 ppm (9.4 mg/kg/day) of formaldehyde on days 4-56 of gestation. No adverse reproductive effects were noted in the formaldehyde-treated group as assessed by the following parameters: pregnancy rate, length of gestation, litter size, growth retardation and survival to weaning. Further, no visceral or skeletal malformations were noted in the progeny of the formaldehyde exposed group. Marks et al. (1980) assessed the effect of formaldehyde on reproduction in mice. In the above study, pregnant albino mice were given formaldehyde by gavage at dose levels of 74, 148, or 185 mg/kg/day on days 6-15 of gestation. At the highest dose (185 mg/kg/day) of formaldehyde, 22 of the 34 pregnant mice died before the 18th day, whereas the 74 and 148 mg/kg/day doses had no significant effect on the pregnant dams. Formaldehyde had no adverse effects on reproductive performance in mice as assessed by the following parameters: number of implants, number of resorptions, fetal deaths and fetal weight. At all dose levels, formaldehyde had no significant effect on the incidence of malformed fetuses. The authors concluded that formaldehyde is not teratogenic to the albino mouse.

Cardiovascular Effects

The effects of formaldehyde on the cardiovascular system of rats have been reported by several investigators (Egle and Hudgins, 1974). Egle and Hudgins investigated the effects of intravenous infusion (0.5, 1.0, 5.0, 10.0, 20 mg/kg) and inhalation exposure [2 mg/ml (2 g/m^3)] of formaldehyde on blood pressure and heart rate in the male Wistar rat. Formaldehyde was also given to rats with altered sympathetic function (pretreatment with phentolamine, an adrenergic blocker or reserpine pretreatment with subsequent adrenalectomy) as well as to atropinized and vagatomized rats. The effects of formaldehyde on blood pressure were as follows: a dose of 0.5 mg/kg caused an increase in blood pressure within 5 second after injection; a dose of 1.0 mg/kg in most instances produced an increase in blood pressure, in some instances depressor responses were noted; at the higher levels ($\geq$ 5 mg/kg) only depressor effects were noted, which was also associated with bradycardia. In rats pretreated with reserpine followed by adrenalectomy, the pressor effects of formaldehyde were less frequent. Furthermore, pretreatment with phentolamine resulted in decreased pressor effects of formaldehyde. The effect of formaldehyde on the heart rate < 20 mg/kg did not alter heart rate significantly; however, a pronounced decrease in heart rate was observed after dosing with 20 mg/kg. In addition, the cardioinhibitory effect of formaldehyde was markedly decreased by atropine pretreatment and abolished by vagotomy.

Skin Irritation and Sensitization

Primary skin irritation and allergic contact dermatitis from formaldehyde is quite common. Allergic contact dermatitis can be caused by contact with formaldehyde, formalin, formaldehyde-releasing agents used in cosmetics, medications, germicides and decomposition of formaldehyde-containing resins. Phillips et al. (1972) studies the dermal response of rabbit and human skin to formaldehyde (10 percent w/v, water) using a variation of the standard Draize rabbit irritancy test. Jordan et al. (1979) examined the formaldehyde threshold response in formaldehyde allergic subjects by applying 0, 30, 60, or 100 ppm of formaldehyde in a methanol-water vehicle for 1 week. The closed patch test method resulted in a response to 30 ppm.

Guidance Development

Currently available animal and human data suggest that the physiological and/or biochemical changes in the cardiovascular and gastrointestinal tract following formaldehyde

exposure are primary indicators of formaldehyde toxicity.

Acceptable dose-response ingestion data are not available from which a guidance level can be derived for a short term formaldehyde exposure. However, in order to have guidelines available to direct a response in the case of a spill or accidental contamination, it has been decided to develop a short-term guidance level for formaldehyde based upon the Yonkman et al. (1941) study in humans.

The adverse effects resulting from daily consumption of 22 mg of formaldehyde in human subjects were mild pharyngeal and gastric discomfort. The subjects initially had received 22 mg of formaldehyde per day for the first 14 days and thereafter the daily dosage of formaldehyde was increased every 7 or 14 days until it had reached 200 mg per day by the final week (thirteenth). The dose of 22 mg of formaldehyde (the minimal effect level in humans) will be used in proposing guidance level and a safety factor of 100 will be applied in the calculation since the observed adverse health effects are based on only two human subjects.

In calculating the guidance level, children are assumed to be exposure subjects, and gastrointestinal absorption of formaldehyde is assumed to be 100 percent in humans.

Accepting 0.314 mg/kg (22 mg/70 kg) as the minimal adverse effect dose, calculation of a guidance level for a 10 kg child, consuming 1 liter of water, are given below:

Calculations:

$$\frac{0.314 \text{ mg/kg} \times 10 \text{ kg}}{1 \text{ liter/day} \times 100} = 0.031 \text{ mg/liter/day}$$

The National Academy of Sciences (NAS, 1979) has suggested that the chronic exposure level for formaldehyde in drinking water be 0.11 mg/liter for an adult. This chronic exposure level for formaldehyde (0.11 mg/liter) is based on the Yonkman et al. (1941) study. It should be pointed out that consideration of this study for deriving a short-term SNARL (1-day/10-day) would have been more appropriate than for a chronic SNARL value because (1) only two subjects had participated in the above study and (2) results of recently completed studies suggest that formaldehyde has carcinogenic potential in laboratory animals.

Analysis

A sensitive fluorometric method for the measurement of formaldehyde has been developed by Belman (1963). The fluoro-

metric method is based on the fluorescence of 3,5-diacetyl-1,4-dihydrolutidine formed from the reaction between acetyl-acetone, ammonia, and formaldehyde (Hantzsch reaction). The minimal detection level is 0.005 ug/ml. The fluorescence is linear from 0.005 ug/ml to 1.0 ug/ml of formaldehyde. The procedure is as follows:

1. Preparation of Reagent: 2M ammonium acetate and 0.02M acetyl-acetone (2,4-pentanedione) at pH 6.0.

2. Reaction of Reagent with Formaldehyde: The reagent is mixed with an equal volume of sample solution containing formaldehyde and the mixture placed in a water bath for 60 minutes at 37° C. Remove samples and cool to room temperature.

3. Fluorescence Measurement: The fluorescence is read after cooling to room temperature. The maxima for fluorescence excitation is 410 nm and for emission 510 nm.

Treatment

The literature concerning information on removal of formaldehyde from ambient water is sparse (Giusti et al. 1974).

Conclusions and Recommendations

The guidance level for formaldehyde in drinking water is proposed for short-term exposure. The potential for carcinogenicity of this chemical has not been considered in developing this guidance level. The short-term guidance level is 0.030 mg/liter for formaldehyde and is based on mild pharyngeal and gastric discomfort in adult subjects.

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