Fact Sheet Date: April 2000

NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for Protection of Human Health and Sources of Potable Water

SUBSTANCE: Formaldehyde **CAS REGISTRY NUMBER:** 50-00-0

AMBIENT WATER QUALITY VALUE: 8 micrograms/liter (8 ug/L)

BASIS: Oncogenic effects (6 NYCRR 702.4)

The health effects of exposure to formaldehyde have been reviewed (ATSDR, 1997; Restani and Galli, 1991; IARC, 1995; US EPA, 1998). Data on the health effects in laboratory animals from chronic exposure to formaldehyde in drinking water (Soffritti et al., 1989; Takahashi et al., 1986; Til et al., 1989; Tobe et al., 1989) were reviewed and critically evaluated. The selected ambient water quality value for formaldehyde (8 ug/L) was derived using the available toxicological data and the procedures outlined in 6 NYCRR 702.2 through 702.7.

SPECIFIC MCL AND PRINCIPAL ORGANIC CONTAMINANT CLASS (702.3)

Formaldehyde does not have a Specific MCL (maximum contaminant level) as defined in 700.1 and is not in a principal organic contaminant class as defined in 700.1. Therefore, a water quality value cannot be derived under 702.3.

ONCOGENIC EFFECTS (702.4)

The human data suggest, but do not establish, a causal relationship between occupational exposure to formaldehyde and certain forms of respiratory tract cancer, including

nasopharyngeal cancer (IARC, 1996; US EPA, 1998). Thus, there is **limited**[1] evidence for the human carcinogenicity of formaldehyde (IARC, 1996; US EPA, 1998).

Chronic exposure to inhaled formaldehyde induces nasal cavity cancers in male and female rats (Kerns et al., 1983; Sellakumar et al., 1985; Tobe et al., 1985). Chronic exposure to formaldehyde in drinking water causes leukemias and gastrointestinal tract tumors in male and female Sprague-Dawley (SD) rats (see below, Soffritti et al., 1989) and forestomach papillomas in male Wistar rats (Takahashi et al., 1986).

Incidences of Cancers in Rats after Chronic Exposure to Formaldehyde in Drinking Water (Soffritti et al., 1989)

Water Concentration (mg/L)	Estimated Dose (mg/kg/day)	Incidence in Rats				
		Total Leukemias				GI Tract
		Males	Females	M & F	M & F	
Exposed for 104 weeks starting at 7 weeks of age						
0	0	4/100	3/100	7/200	0/200	
10	1.3	1/50	2/50	3/100		3/100*
50	6.5	5/50	4/50	9/100*		2/100
100	13	5/50	4/50	9/100*		0/100
500	65	8/50*	4/50	12/100*		0/100
1,000	130	6/50	7/50*	13/100*	2/100	
1,500	195	11/50*	7/50*	18/100*	8/100*	
Exposed for 104 weeks starting at 25 weeks of age						
0	0	0/20	1/20	1/40		0/40
2,500	325	2/18	2/18	4/36		2/36
Exposed for 104 weeks starting as 12-day embryos (transplacental exposure)						
0	0	3/59	3/49	6/108	0/108	
2,500	325	4/36	0/37	4/73		8/73*

* $p < 0.05$ (Fisher's exact test)

In two other chronic studies in Wistar rats, formaldehyde in drinking water induced hyperplasia in cells lining the stomach, but the incidences of stomach tumors or tumors at other sites did not differ significantly between treated and control groups (Til et al., 1989; Tobe et al., 1989).

[1]A positive association has been observed between exposure to formaldehyde and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence (IARC, 1996).

There is **sufficient**[2] evidence for the animal carcinogenicity of formaldehyde (IARC, 1996; US EPA, 1998). Formaldehyde is active in short-term tests indicative of potential oncogenic activity, including tests for gene mutations, deoxyribose nucleic acid (DNA) cross-linking, sister chromatid exchanges, and chromosomal aberrations (ATSDR, 1997; IARC, 1996; Ma and Harris, 1988; US EPA, 1998). Formaldehyde is an oncogen under 700.1(a)(26)(iii) and (v).

The dose-response data (see Table) for total leukemias (i.e., incidence of rats with lymphoblastic leukemias, lymphosarcomas, immunoblastic lymphosarcomas, other leukemias or hemolymphoreticular sarcomas) in male and female SD rats chronically ingesting formaldehyde (Soffritti et al., 1989) were used to derive a water quality value based on oncogenic effects. The incidence data on male and female rats were combined because the incidences in controls and exposed groups did not differ substantially between sexes.

The rats were given drinking water (ad libitum) for 2 years starting at 7 weeks of age. Data on average body weight or water consumption during the study were not provided; thus, values recommended by the US EPA (1987) for SD rats in chronic studies were used to estimate the average daily intake of formaldehyde during the course of the study (Exhibit 1). The Soffritti et al. (1989) study was selected because the route of exposure was oral (drinking water), the study length and sample sizes were adequate for a chronic oncogenicity study, and the survival rates of dosed rats were similar to those of the control rats. The dose-response data for leukemias were selected over the data for gastrointestinal tumors because the dose-response relationship was stronger. Dose-response data for the incidences of rats with a specific leukemia and/or a gastrointestinal tumor were not provided.

A cancer potency factor of 4.2×10^{-3} per milligram body weight per day (4.2×10^{-3} $(mg/kg/day)^{-1}$)) was derived using procedures consistent with those outlined in paragraphs (a) through (e) of 702.4 (Exhibit 1). Without sufficient evidence to support the use of an alternative high-to-low dose extrapolation model or an alternative animal-to-human extrapolation model, the linearized multistage model for extra risk (702.4(a)) and a trans-species scaling factor based on the assumption that human and animal lifetime cancer risks are equal when daily administered doses are in proportion to body weights raised to the 3/4 power (702.4(e)) were used. Assuming a 70-kg adult drinks 2 liters of water per day for an exposure period of 70 years (702.2(c) and 702.4(f)), the water value corresponding to the lower bound estimate on the dose associated with an excess lifetime human cancer risk of one-in-one-million is 8 ug/L (rounded from 8.4 ug/L).

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[2] A causal relationship has been established between formaldehyde and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols (IARC, 1996).

NON-ONCOGENIC EFFECTS (702.5)

Formaldehyde in drinking water damages the stomach and kidney of laboratory animals (ATSDR, 1997; IARC, 1995; Til et al., 1989; US EPA, 1998). In 1990, the US EPA established an oral reference dose (equivalent to an acceptable daily intake) of 200 micrograms per kilogram body weight per day (ug/kg/day) formaldehyde (Exhibit 2, taken from US EPA, 1998), using procedures consistent with those outlined in paragraph (a) and (b) of 702.5. This reference dose, which was rounded from a value of 150 ug/kg/day (US EPA, 1998) was derived by application of a 100-fold uncertainty factor to a no-observed-effect level (NOEL) of 15 mg/kg/day for stomach toxicity (histopathological changes in the lining of the stomach) and reduced weight gain in rats exposed through drinking water daily for 2 years (Til et al., 1989). In developing the reference dose, the US EPA noted that additional chronic bioassays and reproductive and developmental studies support the critical effect and study. ATSDR (1997) derived a chronic oral minimal risk level (also equivalent to an acceptable daily intake) of 200 ug/kg/day, based on the same study and using the same uncertainty factor. A potential ambient water quality value of 1,400 ug/L is derived assuming a 70-kg adult drinks 2 liters of water per day and allowing 20% of the acceptable daily intake (200 ug/kg/day) to come from drinking water (6 NYCRR 702.2(c) and 702.5(c)).

CHEMICAL CORRELATION (702.7)

A value based on chemical correlation was not derived because the toxicity data are sufficient to derive a value based on both oncogenic effects (702.4) and non-oncogenic effects (702.5).

OTHER STANDARDS AND GUIDELINES

Under the New York State Department of Health drinking-water regulations (10 NYCRR Part 5), formaldehyde is an unspecified organic contaminant (UOC) and has a maximum contaminant level (MCL) of 50 ug/L. The World Health Organization (WHO) derived a guideline value of 900 ug/L for formaldehyde in drinking water, assuming a 60-kg adult drinks 2 liters of water per day and allocating 20% of the WHO reference dose (150 ug/kg/day) to drinking water (WHO, 1996). The guideline was based on the same NOEL and study (15 mg/kg/day, Til et al., 1989) as the US EPA reference dose.

SELECTION OF VALUE

According to 702.2(b), the selected ambient water quality value shall be the most stringent of the values derived using the procedures found in 6 NYCRR 702.3 through 702.7. This value is 8 ug/L (based on oncogenic effects) and is the value selected as the water quality value for formaldehyde.

REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Toxicological Profile for Formaldehyde. Atlanta, GA: U.S. Department of Health and Human Services, U.S. Public Health Service.

6 NYCRR (New York State Codes, Rules and Regulations). 1998. Water Quality Regulations, Surface Water and Groundwater Classifications and Standards: Title 6 NYCRR, Chapter X, Parts 700 - 705. Albany, NY: New York State Department of Environmental Conservation.

10 NYCRR (New York State Codes, Rules and Regulations). 1998. Public Water Systems: Title 10 NYCRR, Chapter 1, State Sanitary Code, Subpart 5-1. Albany, NY: New York State Department of Health, Bureau of Public Water Supply Protection.

IARC (International Agency for Research on Cancer). 1995. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Formaldehyde. 62:217-375. Lyon, France: World Health Organization.

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Ma, T-H., and M.M. Harris. 1988. Review of the genotoxicity of formaldehyde. Mutat. Res. 196:37-59.

Restani, P., and C.L. Galli. 1991. Oral toxicity of formaldehyde and its derivatives. Crit. Rev. Toxicol. 21:315-321.

Sellakumar, J.P., C.A. Snyder, J.J. Solomon and R.E. Albert. 1985. Carcinogenicity of formaldehyde and hydrogen chloride in rats. Toxicol. Appl. Pharmacol. 81:401-406.

Soffritti, M., C. Maltoni, F. Maffei and R. Biagi. 1989. Formaldehyde: An experimental multipotential carcinogen. Toxicol. Ind. Health. 5:699-730.

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Til, H.P., R.A. Woutersen, V.J. Feron, V.H.M. Hollanders, H.E. Falke and J.J. Clary. 1989. Two-year drinking water study of formaldehyde in rats. Food Chem.Toxicol. 27:77-87.

Tobe, M., T. Kaneko, Y. Uchida, E. Kamata, Y. Ogawa, Y. Ikeda and M. Saito. 1985. Studies on the Inhalation Toxicity of Formaldehyde. Japan: National Sanitary and Medical Laboratory Service, Toxicity Department of the Organism Safety Research Center.

Tobe, M., K. Naito and Y. Kurokawa. 1989. Chronic toxicity study on formaldehyde administered orally to rats. Toxicology. 56:79-86.

TOX_RISK. 1998. Toxicology Risk Assessment Program. Version 4.0. Developed by K.S. Crump et al. Ruston:LA: The KS. Crump Group, Inc., ICF Kaiser.

US EPA (U.S. Environmental Protection Agency). 1987. Recommendations for and Documentation of Biological Values for Use in Risk Assessment. EPA/600/6-87/008. Cincinnati, OH: Environmental Criteria and Assessment Office.

US EPA (U.S. Environmental Protection Agency). 1998. Formaldehyde. On-line as of May, 1998. Integrated Risk Information System (IRIS). Cincinnati: Office of Research and Development, Environmental Criteria and Assessment Office.

WHO (World Health Organization). 1996. Guidelines for Drinking Water Quality, 2nd ed. Vol. 1: Recommendations. Geneva, Switzerland: World Health Organization. Pp. 837-845.

SEARCH STRATEGY

Toxline (1981 to October, 1998) was searched linking the CAS RN for formaldehyde with the keywords "chronic", “cancer”, “reproductive”, “developmental” and “drinking water.”

Bureau of Toxic Substance Assessment
New York State Department of Health
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EXHIBIT 1. WORKSHEET FOR DERIVATION OF ONCOGENIC VALUE FOR FORMALDEHYDE

1. References

Soffritti, M., C. Maltoni, F. Maffei and R. Biagi. 1989. Formaldehyde: An experimental multipotential carcinogen. Toxicol. Ind. Health. 5: 699-730.

2. Dose-Response Data for High-to-Low Dose Extrapolation Using TOX_RISK Software

Oncogenic Effect	Total leukemias (see text for types) in male and female SD (Sprague-Dawley) rats
Dose Regime	0, 10, 50, 100, 500, 1,000 and 1,500 mg/L in drinking water for 104 weeks
Rat Body Weight	0.43 kg (average of males (0.52 kg) and females (0.34 kg))[1]
Water Consumption	0.13 L/kg/day (average of males (0.062 L/0.52 kg/day) and females (0.045 L/0.34 kg/day)[1]
Daily Doses	0, 1.3, 6.5, 13, 65, 130 and 195 mg/kg/day in drinking water
Incidence[2]	7/200, 3/100, 9/100, 9/100, 12/100, 13/100, and 18/100

[1] Recommended values for Sprague-Dawley rats over the course of a chronic study (US EPA, 1987. Recommendations for and Documentation of Biological Values for Use in Risk Assessment. EPA/600/6-87/008. Cincinnati, OH: Environmental Criteria and Assessment Office.)

[2] Denominator is number of animals at the start of the experiment.

3. Derivation of Cancer Potency Factor

Lower Bound on Dose Corresponding to Excess Lifetime Risk of One-in-One Million

Rat daily dose	= 0.86 ug/kg/day (TOX_RISK (linearized multistage model) estimate of 95% lower bound on dose associated with 1×10^{-6} incidence)**
Human daily dose	= 0.24 ug/kg/day = 0.86 ug/kg/day x $(0.43 \text{ kg}/70 \text{ kg})^{0.25}$
Cancer potency factor	= 1×10^{-6} risk level/1×10^{-6} human dose (0.24 ug/kg/day)
	= 4.2×10^{-6} per ug/kg/day = 4.2×10^{-3} per mg/kg/day

**using a simple linear model gives 0.90 ug/kg/day for dose associated with an 1×10^{-6} incidence (i.e., 95% lower bound on dose (90,000 ug/kg/day) associated with a 0.1 incidence / 100,000).

4. Derivation of Ambient Water Quality Value

Water value	= (0.24 ug/kg/day x 70 kg)/2 L/day = 8 ug/L

EXHIBIT 2: ORAL REFERENCE DOSE SUMMARY FOR FORMALDEHYDE (CAS REGISTRY NUMBER 50-00-0): TAKEN FROM THE WORLDWIDE WEBSITE FOR THE INTEGRATED RISK INFORMATION SYSTEM OF THE U.S. ENVIRONMENTAL PROTECTION AGENCY (AS OF DECEMBER 1998)

___I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Formaldehyde
CASRN -- 50-00-0
Last Revised -- 09/01/90

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Reduced weight gain, histopathology in rats	NOAEL: 15 mg/kg/day	100	1	2E-1 mg/kg/day
	LOAEL: 82 mg/kg/day			
Rat 2-Year Bioassay Til et al., 1989				

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* Conversion Factors: none

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Til, H.P., R.A. Woutersen, V.J. Feron, V.H.M. Hollanders, H.E. Falke and J.J. Clary. 1989. Two-year drinking water study of formaldehyde in rats. Food Chem. Toxicol. 27: 77-87.

Formaldehyde was administered daily in drinking water to Wistar rats (70/sex/dose) for up to 24 months at mean doses of 0, 1.2, 15, or 82 mg/kg/day for males and 0, 1.8, 21, or 109 mg/kg/day for females. Up to 10 rats/sex/dose were sacrificed and examined after 12 months and 18 months of treatment; the remainder was sacrificed and examined at 24 months. Mean body weights of the high-dose group were decreased in males from week 1 and in females from week 24 through termination. Food intake was significantly decreased in all high-dose males with females showing a similar but less consistent decrease in food intake. A 40% decrease in drinking water intake was reported in all high-dose animals while those rats receiving the middle dose showed a slight but generally insignificant decrease in liquid intake. Changes in urinalyses, and hematological and clinical chemistry parameters, were not dose-related, so were not considered to be related to formaldehyde intake. Among the high-dose males, significant decreases were seen in the absolute heart and liver weights at 18 months and at termination; in testes weights at 18 months; and in

kidney weights at termination. High-dose females showed significant increases in the relative kidney weights at 12 and 24 months.

Relative brain weights were significantly increased in high-dose males at all three examination periods and in females at termination only. Relative testes weights were significantly increased in high-dose males at termination. These relative organ weight increases were generally ascribed to the decreased body weights observed. A significant increase in mortality among males receiving the 15 mg/kg/day dose was not considered toxicologically significant.

Gross examination at 12, 18, and 24 months revealed a raised, thickening of the limiting ridge of the forestomach in most high-dose rats and in some rats of both sexes from other groups. Irregular mucosal thickening of the forestomach and glandular stomach were seen in several rats of the high-dose group and in occasional rats of other groups. The incidence of discoloration and irregularity of the kidney surface and atrophy of the testes was lower in the high-dose group as compared with controls.

Significant histopathological changes of the gastrointestinal tract were found in high-dose males and females and included chronic atrophic gastritis of the glandular stomach from week 53 on, as well as focal ulceration and glandular hyperplasia at the terminal examination. The incidence of focal papillary epithelial hyperplasia and focal hyperkeratosis of the forestomachwas significantly increased in both sexes at the terminal examination. These effects of formaldehyde on the gastric mucosa were considered cytotoxic in nature. A significant increase in the incidence of papillary necrosis of the kidneys was reported in both sexes of high-dose rats at the terminal examination. No treatment-related gastric tumors were observed in this study. The incidence and type of tumors observed in other organ systems were common to this strain and similar to those found in aging rats, 30 were not considered toxicologically significant. A NOAEL of 15 mg/kg/day in male rats was indicated in this study.

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF -- An uncertainty factor of 100 was used to account for the inter- and intraspecies differences.

MF -- None

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- High
Data Base -- Medium
RfD -- Medium

Confidence in the critical study is high since it consisted of adequate numbers of animals of both sexes, as well as a thorough examination of toxicological and histological parameters.

Confidence in the data base is medium as several additional chronic bioassays and reproductive and developmental studies support the critical effect and study. Medium confidence in the RfD follows.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- U.S. EPA, 1989
Other EPA Documentation -- None
Agency Work Group Review -- 11/17/89, 05/17/90, 06/20/90
Verification Date -- 06/20/90