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NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

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

SUBSTANCE: Acetaldehyde **CAS REGISTRY NUMBER**: 75-07-0

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

BASIS: Chemical Correlation (6 NYCRR 702.7)

Data on the potential health effects of exposure to acetaldehyde have been reviewed (Feron et al., 1991; IARC, 1985; US EPA, 1987). The selected ambient water quality value for acetaldehyde (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)

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

However, the New York State Department of Health (10 NYCRR Part 5) does have a MCL of 50 ug/L for acetaldehyde, based on its categorization as an unspecified organic contaminant (UOC). This DOH general MCL applies as a drinking water standard to any substance that is not in a POC class and does not have a Specific MCL. However, this UOC MCL is not used as the basis for an ambient water quality value under 702.3.

ONCOGENIC EFFECTS (702.4)

The human data are inadequate to evaluate the human carcinogenicity of acetaldehyde (IARC, 1985; US EPA, 1998a). Chronic exposure to inhaled acetaldehyde caused nasal cavity tumors in rats and hamsters and laryngeal tumors in hamsters (Feron et al., 1982; IARC, 1985; US EPA, 1998a; Woutersen et al., 1986). Data on the oncogenic effects of acetaldehyde in drinking water are limited to one study that found hyperplastic and hyperproliferative changes in the epithelia of the upper gastrointestinal tract (i.e., the tongue, epiglottis and forestomach) of 10 rats exposed via drinking water for 8 months (Homann et al., 1997). These changes included increased epithelial thicknesses and proliferation indices, but the incidences in control and dosed rats were not reported. Similar types of hyperplastic lesions, and more importantly, oncogenic lesions were found in the epithelial cells of the nasal passages of rats chronically exposed to acetaldehyde in air (Feron et al., 1982 al., 1982; Woutersen et al., 1986). Acetaldehyde also is active in short-term tests indicative of potential oncogenic activity, including tests of deoxyribonucleic acid (DNA) cross-linking (Ristow and Obe, 1978), sister chromatid exchanges, micronuclei formation, and chromosomal aberrations (Feron et al., 1991; IARC, 1985; US EPA, 1998a). Overall, there is **sufficient**[1] evidence for the animal carcinogenicity of acetaldehyde (IARC, 1985; US EPA, 1998a). Acetaldehyde is an oncogen under 700.1(a)(26)(ii) and (v).

The dose-response data from Homann et al. (1997) cannot be used for high-to-low dose extrapolation because data on the incidences of rats with hyperplastic or hyperproliferative changes were not provided. Dose-response data describing the relationship between air concentration and nasal tumor incidences in rats (Feron et al., 1982; Woutersen et al., 1986) were not considered appropriate for use in estimating potency via the oral route given the uncertainties associated with extrapolating the dose at the nasal epithelium to a dose at the stomach or intestinal epithelium. Moreover, oral doses of acetaldehyde may have oncogenic effects outside in the gastrointestinal tract. Thus, the dose-response data on the oncogenic effects of acetaldehyde are inadequate to estimate the oncogenic potency of acetaldehyde via the oral route.

NON-ONCOGENIC EFFECTS (702.5)

Chronic studies on the oral toxicity of acetaldehyde in laboratory animals were not found. Limited data from four oral subchronic toxicity of acetaldehyde in animals indicate that the organs/organ systems that appear to be most sensitive to exposure include the

[1] A causal relationship has been established between acetaldehyde 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, 1985).

gastrointestinal tract, the liver, and the kidneys (Bankowski et al., 1993; Homann et al., 1997; Matysiak-Budnik et al., 1996; Til et al., 1988). The effects of acetaldehyde on the liver is expected given that acetaldehyde is the first metabolite of ethanol and is thought to play a direct role in the hepatotoxicity of ethanol (Lieber, 1998; Matysiak-Budnik et al., 1996). There are no data on the reproductive/developmental toxicity of ingested (or inhaled) acetaldehyde (US EPA, 1998a), although there is evidence that intraperitoneal or intravenous injections of acetaldehyde are fetotoxic and teratogenic in rats and perhaps mice (IARC, 1985; US EPA, 1987).

Of the four subchronic oral studies (Table 1), the data from Bankowski et al. (1993) were used to derive a water quality value based on non-oncogenic effects. This study was selected because rats were exposed for 6 months and an adequate number of rats were evaluated (60 dosed and 60 control rats). Moreover, liver collagen is also induced by ethanol, and acetaldehyde is the first metabolite of ethanol. The effect also was detected at a dose lower than those associated with the other effects.

If an uncertainty factor of 3,000 is applied to 60 mg/kg/day, the lowest observed effect level identified in Bankowski et al. (1993), a potential acceptable daily intake of 20 ug/kg/day can be derived for acetaldehyde using procedures consistent with those outlined in paragraphs (a) and (b) of 702.5. Under 702.5(a), an uncertainty factor of 3 was used because the study used to derive the acceptable daily intake identified a minimal effect level rather than a NOEL. A factor of 3 was selected because the observed effects were mild (increased collagen content of the liver). Under 702.5(b)(3), an uncertainty factor of 1,000 was selected because the acceptable daily intake is based on the results from a subchronic animal study and neither experimental results from prolonged exposures of humans nor valid results of long-term ingestion studies on experimental animals are available. A water value of 140 ug/L is derived assuming a 70-kg adult drinks 2 liters of water per day and allowing 20% of the acceptable daily intake (20 ug/kg/day) to come from drinking water (702.2(c) and 702.5(c)).

CHEMICAL CORRELATION (702.7)

Qualitatively, the data on the oncogenic effects of acetaldehyde are sufficient to conclude that it is an oncogen under 700.1. Quantitatively, dose-response data on the oncogenic effects of oral doses of acetaldehyde are not sufficient to use as a basis for an estimate of the oncogenic potency of oral doses of acetaldehyde.

The chemical structure, metabolism, and toxic effects of acetaldehyde are similar to those of formaldehyde (Morris et al., 1996), an oncogen under 700.1 (NYS, 1999). Both chemicals are low-molecular weight, short-chain, aliphatic, saturated aldehydes. Both are highly reactive chemicals, and their reactivity is dependent on the electrophilic aldehyde group. Both are efficiently absorbed and distributed, and metabolized by the same enzymes (aldehyde dehydrogenases). Both chemicals induce toxicity at the site-of-contact in the respiratory tract

after inhalation and in the digestive tract after ingestion. The general nature of the lesions are also similar: tumors and/or hyperplasia. Moreover, both chemicals are active in the same short-term tests indicative of oncogenic activity, including the formation of protein-DNA cross-links, which may play an important role in their toxicity.

Available data, however, also suggest that the structural differences between formaldehyde and acetaldehyde lead to different responses in exposed animals. Qualitatively, for example, rats inhaling acetaldehyde develop nasal squamous cell carcinomas and adenocarcinomas whereas rats inhaling formaldehyde develop almost exclusively nasal squamous cell carcinomas (Woutersen et al., 1986). Quantitatively, acetaldehyde and formaldehyde may have different potencies to induce site-of-contact toxicity in the respiratory tract after lifetime exposure or in the gastrointestinal tract after less-than-lifetime exposures.

The potency of inhaled acetaldehyde to induce of nasal tumors appears less than that of formaldehyde (Table 2). However, the relative difference varies with potency index and ranges from 4-fold to 29-fold. Moreover, the uncertainties in understanding the route-specific differences in the pharmacokinetics and pharmacodynamics of inhaled versus ingested doses precludes confidently estimating the relative differences in the oncogenic potencies of oral doses of the two chemicals based on the relative differences in oncogenic potencies of inhaled doses.

Short-term studies indicate that ingested acetaldehyde may be five-times less potent stomach toxicant than ingested formaldehyde (Table 2, acetaldehyde LOELs/formaldehyde LOELs = 5). However, the use of these differences to estimate the relative differences between the oncogenic potencies of the two chemicals is precluded by the lack of understanding of the relationships between short-term effects and oncogenic effects.

The results of three other studies (Table 3) provide information useful for determining whether relative differences in the oncogenic potencies of ingested acetaldehyde and formaldehyde to induce gastrointestinal-tract tumors can be estimated from ingestion studies of pre-oncogenic, proliferative changes in the gastrointestinal tract. Rats in these studies were exposed for 8 to 12 months via drinking water and the epithelial cells lining the forestomach were examined for hyperplasia. Thus, the type and length of exposure and the type of lesions examined were similar to those of a long-term oral oncogenicity study. However, only the formaldehyde studies identified a NOEL (50 mg/kg/day) and a LOEL (82 mg/kg/day); the acetaldehyde study was a single-dose study that detected hyperplasia at the only dose tested (324 mg/kg/day). Without a dose-response curve for acetaldehyde, there is no direct evidence to quantify the differences in the relative potencies of ingested acetaldehyde and formaldehyde to induce stomach hyperplasia. Thus, these data are inadequate to assess the relative potencies of the two compounds to cause oncogenic effects in the gastrointestinal tract. In addition, confidence in any estimates would be limited because factors besides hyperplasia are involved in the oncogenic process and the correlation between potencies for hyperplasia and for gastrointestinal tumors are unknown.

Formaldehyde induces cancers (leukemias) at sites other than the site-of-contact (Soffritti et al., 1989). It is likely that the systemic effects of the formaldehyde and acetaldehyde would be similar given their qualitative similarities in chemical structure, metabolism, and toxic effects at point-of-contact. There are no data to dismiss concerns that acetaldehyde would be leukogenic when tested in a lifetime oral oncogenic study, and no data to assess the relative differences in the potency of the two chemicals to cause oncogenic effects beyond the site-of-contact. An ambient water quality value of 8 ug/L has been derived for formaldehyde based on its oncogenic effects (total leukemias in male and female rats) after oral lifetime exposures (NYS, 1999).

There is sufficient qualitative evidence to conclude that formaldehyde is a reasonable surrogate for acetaldehyde. Some toxicity data suggest that formaldehyde is a more potent toxicant than acetaldehyde, but the use of these data to estimate quantitative differences in the oncogenic potency of lifetime oral doses of acetaldehyde and formaldehyde are limited by concerns over extrapolating results from inhalation studies or short-term studies and by data gaps in the toxicity data on acetaldehyde. In the absence of good quantitative data on the differences in the oncogenic potencies of lifetime oral doses of formaldehyde or acetaldehyde, they were assumed to be equipotent. Thus, an ambient water quality value of 8 ug/L is derived for acetaldehyde based on its chemical correlation to formaldehyde.

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 702.3 through 702.7. This value is 8 ug/L (based on chemical correlation) and is the value selected as the water quality value for acetaldehyde.

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SEARCH STRATEGY

Toxline (1981 to April, 1998) was searched linking the CAS RN for acetaldehyde with the keywords chronic, cancer, subchronic, genotoxicity and drinking water. The search was updated in October, 1998 by searching Medline and Toxline (1997-May 1999) for papers on acetaldehyde.

Bureau of Toxic Substance Assessment
New York State Department of Health
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Table 1. Drinking Water Studies in Rats: NOELs and LOELs.

Study	Duration of Exposure	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Effects*
Homann et al. (1997)	8 months	none	324**	hyperplastic and hyperproliferative changes in upper gastrointestinal tract
Bankowski et al. (1993)	6 months	none	60**	increased collagen content of liver
Matysiak-Budnik et al. (1996)	11 weeks	120	500	fatty liver and inflammatory changes in liver
Til et al. (1988)	4 weeks	125	675	hyperkeratosis of the forestomach

* all changes statistically significant ($p < 0.05$)
** only dose tested

Table 2. Relative Potency of Acetaldehyde Compared to Formaldehyde.

Response Parameter	Ratio of Acetaldehyde To Formaldehyde	Source
Air Exposure (nasal tumors in rats)		
US EPA unit risk factors	0.16 (acetaldehyde 6-times less potent)	US EPA, 1999a,b
LED_{10}[1] (delivered dose)[2]	4.3 (acetaldehyde dose 4-times higher)	See footnotes
LED_{10}[1] (administered dose)[3]	29 (acetaldehyde dose 29-times higher)	See footnotes
Oral Exposure		
LOELs (hyperkeratosis of rats stomach after 4-week drinking water exposure)	5.4 (acetaldehyde dose 5-times higher)	Til et al., 1988
Level of indirect estimator of DNA-protein cross-links after single oral dose	5 (the level of the indirect estimator induced by acetaldehyde was about 5-times lower	Morris et al., 1996

[1] lower bound on the effective dose associated with a 10% incidence of nasal tumors in male rats (combined incidence of squamous cell carcinomas and adenocarcinoma for formaldehyde (Kerns et al., 1983) and acetaldehyde (Woutersen et al., 1986))

[2] delivered doses (mg/cm^2 nasal surface area/day) taken from Morris et al. (1996)

[3] administered doses are equal to experimental exposure levels (0, 750, and 1,500 ppm for acetaldehyde (Woutersen et al., 1986) and 0, 2, 5.6, and 14.3 ppm for formaldehyde (Kerns et al., 1983) for 6 hours/day, 5 days/week) corrected to continuous exposure

Table 3. Chronic Drinking Water Studies on Rats: Forestomach Hyperplasia.

Chemical & Results	Dose (mg/kg/day)	Endpoint*	Length of Exposure	Study
Acetaldehyde				
epithelial hyperplasia (increased epithelial thickness of forestomach)	324	effect level**	8 months	Hodman et al. (1997)
Formaldehyde				
Squamous cell hyperplasia of of forestomach	300	LOEL***	12 months	Tobe et al. (1989)
	50	NOEL		
Formaldehyde				
focal papillary epithelial hyperplasia of forestomach	82 - 109	LOEL***	12 months	Til et al. (1989)
	15 - 21	NOEL		

* significant differences ($p < 0.05$) at LOELs
** only dose tested
*** highest dose tested