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NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for Protection of Sources of Potable Water

SUBSTANCE(S): *CHLOROFORM* **CAS REGISTRY NUMBER(S):** 67-66-3

AMBIENT WATER QUALITY VALUE: 7 ug/L

BASIS: Oncogenic effects (702.4)

SUMMARY OF INFORMATION:

The toxicity of chloroform has been reviewed by the National Academy of Sciences (NAS) (1980, 1978, 1977), United States Environmental Protection Agency (USEPA) (1980), International Agency for Research on Cancer (IARC) (1979), and others (Davidson et al., 1982 and Bull, 1985, 1982). As the predominant trihalomethane (THM) in chlorinated water, chloroform has been the focus of a number of epidemiological studies evaluating relationships between drinking water chlorination practices and health statistics (NAS, 1980).

The following is a brief summary of the available toxicological information regarding potential human health effects associated with exposure to chloroform in drinking water.

I. Pharmacokinetics

Chloroform is readily absorbed via the respiratory system and to a lesser extent by the gastrointestinal tract. It distributes rapidly to the blood, brain, kidney and lung and concentrates primarily in the body fat and liver. Unmetabolized chloroform is excreted readily in expired air.

Chloroform metabolism is species and concentration dependent and occurs mainly in the kidney and liver. At high body burdens, the extent of metabolism is approximately 30 to 40 percent for humans and greater than 65 percent and 85 percent for rats and mice, respectively (Davidson et al., 1982). The breakdown of chloroform is thought to proceed through the formation of methylene chloride, formaldehyde and formic acid to carbon dioxide and the chloride ion. Reactions catalyzed by the microsomal enzyme system lead to a very

reactive metabolite, phosgene, which may be one of the toxicants associated with chloroform toxicity. Smith et al. (1984) attributed greater chloroform sensitivity in male mice than female mice to higher phosgene production rates demonstrated for male mice.

2. Acute/Chronic Toxicity

Chloroform is considered to be moderately toxic. Toxicity associated with exposure by inhalation appears to be greater than by ingestion. In animals, acute toxicity has been shown to be species, strain, sex and age dependent, with oral LD_{50}s in the range of 120 to 1188 mg/kg (IARC, 1979). In humans, chloroform exposure has been fatal, with death attributed to cardiac arrest and liver and kidney damage. Symptoms of chronic exposure include respiratory and neurological effects as well as kidney and liver damage.

3. Synergism/Antagonism

The toxic effects of chloroform are enhanced in animals that have been pretreated with alcohols, barbiturates, and certain other chemical agents (USEPA, 1980).

4. Teratogenic and Reproductive Effects

Mode of exposure appears to play a role in the teratogenic potential of chloroform. Although chloroform has not been shown to be teratogenic in animal ingestion studies (Ruddick et al., 1983), inhalation studies using rats and rabbits have shown embryotoxic effects, such as fetal abnormalities, reduced birth weight and fetal mortality (IARC, 1979).

5. Mutagenicity

In vitro mutagenicity tests using bacterial and mammalian cells, with and without metabolic activition, have been negative. Results of in vivo studies, however, suggest that chloroform is a pro-mutagen (Davidson et al., 1982; Bull et al., 1985).

6. Carcinogenicity

Chloroform has been shown to induce tumors at different organ sites in several strains of rats and mice in a number of independent bioassays using a variety of dosing methods. The carcinogenic effects of chloroform were first recognized by Eschenbrenner and Miller (1945) in Strain A mice given intragastric doses of chloroform in olive oil. Tumors were observed in the kidneys of males and in the liver of both sexes. In 1976 the National Cancer Institute (NCI) reported results of a cancer bioassay in which B6C3F1 mice and Osborne-Mendel rats were administered chloroform in corn oil by gavage. This study reported that chloroform was capable of inducing liver tumors in both sexes of mice, as shown by previous studies, and kidney tumors in the male rat (NCI, 1976). Roe et al. (1979) observed kidney tumors in one of four strains of mice but not in Sprague-Dawley rats administered chloroform in a toothpaste base. Tumasonis et al. (1985) reported a significant increase in

liver tumors in female Wistar rats exposed to chloroform in drinking water throughout their lifetime.

Results of a chloroform carcinogenesis bioassay conducted at Stanford Research International were published by Jorgensen et al. (1985). Chloroform was administered to male Osborne-Mendel rats and female B6C3F1 mice at multiple dose levels in drinking water for 104 weeks. Kidney tumors were observed in the male rats at a slightly lower incidence rate than in the NCI study, but in the mice no treatment-related increases in tumor incidence were observed.

Reitz et al. (1982) investigated the role of genetic and non-genetic mechanisms in chloroform carcinogenicity in B6C3F1 mice and concluded that the primary mechanism of chloroform-induced carcinogenesis is non-genetic. Pereira et al. (1985) were unable to demonstrate chloroform tumor-promoting activity in mice, but Deml and Oesterle (1985) demonstrated that chloroform is a liver cancer promoting agent in female Sprague-Dawley rats administered chloroform in olive oil by gavage.

7. Epidemiology

No long-term studies on occupational exposure to chloroform are available. The NAS evaluated EPA-conducted drinking water surveys and cancer statistics and concluded that there was insufficient information to confirm any hypothesized relationship between chloroform or THMs and cancer rates. Although some studies evaluated by the NAS suggested that higher concentrations of THMs in drinking water may be associated with an increased frequency of bladder cancer, the association was small and margin of error was large (NAS, 1980). More recently, Lawrence et al. (1984) were unable to demonstrate a relationship of THM to colorectal cancer in white female teachers in New York State.

DERIVATION OF VALUES:

The toxicological information was evaluated with respect to deriving an ambient water quality value pursuant to Part 701 (proposed Part 702) methodologies. Because chloroform has been shown by several independent studies to induce tumors at several sites and in two mammalian species, it satisfies the criteria set forth in the definition of an oncogenic chemical in subdivision 701.1(p) (proposed Part 700). Therefore, a value for chloroform should be derived using the section 701.4 (proposed section 702.3) procedure which is based on oncogenic effects. This value would be more stringent than any derived by other Part 701 (proposed Part 702) procedures based upon protection of human health.

I. Other Quantitative Risk Assessments

Quantitative risk assessments have been performed for chloroform by the NAS (1978), USEPA (1980), and New York State Department of Health (DOH) (1984) (see Table 1). The NAS calculated both the point estimate of risk and its upper 95 percent confidence limit for consumption of water at a chloroform concentration of 1 ug/l per day using several individual data sets reported in both the Roe et al. (1979) and the NCI (1976) bioassays. Both the EPA and DOH reported the water quality value associated with the lower 95 percent confidence limit on the 1×10^{-6} excess cancer risk derived from the most sensitive data set (i.e., liver tumors in female mice) from the NCI (1976) results.

Table 1. Summary of Drinking Water Values Derived for Chloroform

Source	Data Set	Value (ug/l) Risk Estimate (2)	95% LCL (3)
National Academy of Sciences (1978) (1)	NCI (1976) rodents fed chloroform in corn oil:		
	O-M Rat male (kidney)	3	2
	O-M Rat female (kidney)	30	6
	B6C3F1 mouse male (liver)	"poor fit"	0.4
	B6C3F1 mouse female (liver)	0.3	0.2
	Roe et al. rodents fed chloroform in toothpaste base:		
	Rat female (total)	2	0.7
	CF/1 mouse male (liver)	9	1
	Swiss mouse male (liver)	2	0.7
United States Environmental Protection Agency (1980)	NCI (1976) liver tumors in B6C3F1 female mice fed chloroform in corn oil	---	0.19
New York State Department of Health (1984)	NCI (1976) liver tumors in B6C3F1 female mice fed chloroform in corn oil	---	0.2

(1) NAS (1978) risk estimates at 1 ug/l day for 70 kg humans are converted to drinking water values associated with 1 x 10-6 excess cancer risk and consumption of 2 l/day

(2) Estimate of drinking water value associated with 1 x 10-6 excess cancer risk based on maximum-likelihood-estimate

(3) 95% lower confidence limit on (2)

Past risk assessments for chloroform were largely based upon the incidence of tumors in the mouse liver. Use of mouse liver tumor data in quantitative risk assessment has been controversial because of observed high spontaneous background tumor incidence (OSTP, 1985). In addition, possible effects of corn oil, used in the NCI gavage studies, on both chloroform absorption and tumor incidence in the mouse liver have been hypothesized (Newberne et al., 1979).

The USEPA has recommended that mouse liver tumors be given special consideration but not ignored as an indicator of carcinogenicity (USEPA, 1985). Therefore, use of other tumor data may be more biologically acceptable than mouse liver data for quantitative risk assessment. Treatment-related tumor responses were observed in the kidney of the male Osborne-Mendel rat in both the NCI (1976) and Jorgensen et al. (1985) studies. The occurrence of tumors in the kidney of this strain of rat is rare, particularly in the female (Gart et al., 1979).

2. Selection of Data

Data sets from the Jorgensen et al. (1985) study were evaluated with respect to deriving an ambient water quality value for chloroform by the procedures set forth in section 701.4 (proposed section 702.3). A statistically significant increase in tumor incidence was observed only in the kidney of the male Osborne-Mendel rat (Table 2). The kidney tumor data selected are comprised of the combined incidence of tubular cell adenomas and adenocarcinomas, or benign and malignant tumors. The overall observed contribution of malignant tumors to the total of all kidney tumors in this study was 37 percent.

Table 2. Kidney Tumor Data for Male Osborne-Mendel Rat (1)

Source	Exposure	Dose (2) (mg/kg/da)	Incidence	
Jorgensen et al. (1985)	Drinking water for 104 weeks	0	1/50	(2%)
		19	4/313	(1%)
		38	4/148	(3%)
		81	3/48	(6%)
		160	7/50	(14%)*

(1) Adenomas and adenocarcinomas of tubular cell origin
(2) Average daily intake during lifetime

* Statistically different from control group at $p < 0.05$

The NCI (1976) study also reported a statistically significant increase in kidney tumors in the male Osborne-Mendel rat. For the purpose of risk assessment, however, results of the NCI study are considered less appropriate than the Jorgensen study for a number of reasons. Use of the NCI data requires the assumption that high doses over a short period are equivalent to lower doses over a longer period of time. The NCI results may have been confounded by possible effects of oral gavage related to both the single high-concentration doses and the corn-oil vehicle. The Jorgensen study, however, used a more desirable method of exposure by continuously dosing animals with chloroform dissolved in drinking water over their lifetime. In addition, this study allowed for an improved definition of the dose-response relationship by using twice as many dose levels and larger adjusted animal group sizes.

3. Selection of Model

For the derivation of an ambient water quality value, Part 701 (proposed Part 702) specifies use of a linear multi-stage (LMS) low-dose extrapolation model unless there is sufficient scientific evidence that supports use of another extrapolation procedure. The LMS model was used by the NAS, USEPA and DOH to derive the water quality values for chloroform presented in Table 1. The available information suggesting chloroform is a non-genotoxic, or threshold, carcinogen is not adequate to support use of a non-linearized model for a value setting.

The dose from which the chloroform value is derived is estimated with the GLOBAL82 LMS extrapolation model (Howe and Crump, 1982). Both the 95 percent lower confidence limit (LCL) and maximum likelihood estimate (MLE) are calculated on the dose associated with 1 x 10-6 excess lifetime cancer risk. The confidence limit provides a water quality value that is 95 percent certain to be more stringent than the value associated with the true risk, while the MLE should have the best association with true
risk, which may be as low as zero.

4. Conversions

The output of the GLOBAL82 model, which is the animal dose associated with a 1 x 10-6 excess cancer risk, is presented in Table 3. The animal dose is converted to a human dose by the surface-area conversion rule as specified in section 701.4 (proposed section 702.3), because available pharmacokinetic information does not support an alternative conversion procedure. Human daily doses are then converted to drinking water values that are based on lifetime exposure of a 70-kg human consuming 2 liters of water per day (Table 3). Conversion to human daily dose does not specifically take into account the differences in metabolic rates reported for humans and rats.

Table 3. Values for Chloroform Derived by Section 701.4 Methodology

Data Set (1)	Animal Dose (2) (ug/kg/da) 95% LCL	MLE	Value (ug/l) (3) 95% LCL	MLE
Kidney tumors in Osborne-Mendel male rat (Jorgensen et al., 1985)	1.1	9.7	7	70

(1) Average rat weight = 0.50 kg

(2) Determined by GLOBAL82 for 1 x 10-6 excess cancer risk from animal tumor data: LCL = lower confidence limit; MLE = maximum likelihood estimate

(3) Drinking water value = animal dose x $\frac{\text{animal body weight}}{\text{human body weight}}$ $\frac{0.33 \times 70 \text{ kg}}{2 \text{ l}}$
(ug/kg/da)

5. Uncertainty of Value

The Jorgensen et al. (1985) study provides data for derivation of a water quality value for chloroform that is a more scientifically valid value because of the improved study design, more relevant exposure route, and type of tumor observed.

6. Selection of Value

The value recommended for promulgation as a water quality value for chloroform on the basis of human-health protection is 7 ug/l. This value is based upon the incidence of kidney tumors in male Osborne-Mendel rats exposed to chloroform in drinking water and calculated according to section 701.4 (proposed section 702.3) methodologies.

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