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NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for Protection of Sources of Potable Water

SUBSTANCE: Methyl tert-Butyl Ether (MTBE) **CAS REGISTRY NUMBER:** 1634-04-4

AMBIENT WATER QUALITY VALUE: 10 micrograms/liter (10 ug/L)

BASIS: Oncogenic Effects

INTRODUCTION

Data on the health effects from exposure to MTBE in drinking water or food were not found (ATSDR, 1996; Clary, 1997; HEI, 1996; NRC, 1996; NSTC, 1996, 1997; Stern and Tardiff, 1997; US EPA, 1997). Data on the health effects of oral doses of MTBE are limited (Belpoggi et al., 1995, 1997, 1998; Robinson et al., 1990). Additional information on the chronic, reproductive, and developmental effects of oral exposures to MTBE is needed before the human risks from MTBE in drinking water can be fully evaluated. The database on the effects of inhaled MTBE (ATSDR, 1996; Clary, 1997; HEI, 1996; NRC, 1996; NSTC, 1996, 1997; Stern and Tardiff, 1997; US EPA, 1997) is more extensive than that on the effects of oral exposure. Qualitatively, the absorption, pharmacokinetics, metabolism, elimination, and target organs of ingested and inhaled MTBE appear similar (ATSDR, 1996; Clary, 1997; Dourson and Felter, 1997; NSTC, 1996; US EPA, 1997). Thus, both oral and inhalation data were used to provide a perspective on the human risks from oral exposures to MTBE.

The selected ambient water quality for MTBE (10 ug/L) was derived using the available toxicological data (see bibliography) and the procedures outlined in 6 NYCRR 702.2 through 702.7.

SPECIFIC MCL AND PRINCIPAL ORGANIC CONTAMINANT CLASS (702.3)

MTBE does not have a Specific MCL (maximum contaminant level) for New York State 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 MTBE, 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)

MTBE induced liver tumors in male and female mice after inhalation exposures, kidney tumors in male rats after inhalation exposures, testicular tumors in male rats after inhalation exposures or gavage doses, and lymphomas/leukemias in female rats after gavage doses. (Belpoggi et al., 1995, 1997, 1998; Bird et al., 1997; HEI, 1996; NSTC, 1996, 1997; US EPA, 1997). MTBE is an oncogen under 700.1(a)(26)(ii).

The dose-response data for testicular tumors (interstitial cell adenomas) in male Sprague-Dawley rats given gavage doses of MTBE (Belpoggi et al., 1995, 1997, 1998) were used to derive a water quality value based on oncogenic effects. Male rats (60/dose level) were given a gavage MTBE dose of 0, 250 mg/kg, or 1,000 mg/kg on 4 days/week for 104 weeks (beginning at 8 weeks of age), and maintained until a natural death (the last animal died at 174 weeks of age). The first testicular tumor was observed at 96 weeks of age, and the number of testicular tumors observed in the control, low-dosed, and high-dosed groups were 3, 5, and 11, respectively. Only the animals alive at 96 weeks of age (26, 25, and 32 animals in the control, low-dosed, and high-dosed groups, respectively) were considered at risk for testicular tumors; thus, dose response data corrected for early deaths (i.e., 3/26, 5/25, and 11/32 for the control, low-dosed, and high-dosed groups, respectively) were selected to derive a water quality value.

These dose-response data were selected over other data on the oncogenicity of MTBE because the route of exposure was oral, the length of exposure was 104 weeks, the survival of exposed groups was similar or greater than that of the control group, and there was no evidence that the maximum tolerated dose was exceeded. Two other factors were also important. (1) Statistical analysis by Belpoggi et al. (1995), which adjusted for the influence of the increased survival (post 88 weeks) of high-dosed males on tumor incidences, found a significant increase ($p < 0.05$) in the incidence of testicular tumors in high-dosed males. (2) The induction of testicular tumors by MTBE was observed in a second, independent study conducted with different strain of male rats (F344) and a different route of exposure (inhalation).

A cancer potency factor of 3.4×10^{-3} per milligram per kilogram body weight per day

(3.4×10^{-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 scientific 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 (702.4(f) and 702.2(c)), the water concentration corresponding to the lower bound estimate on the dose associated with an excess lifetime human cancer risk of one-in-one million is 10 ug/L.

This value (10 ug/L) is supported by values based on other dose-response data on the oncogenicity of MTBE after oral or inhalation exposures (Belpoggi et al., 1995, 1997, 1998; Bird et al., 1997). NYS DOH also derived a value of 10 ug/L from dose-response data for leukemias/lymphomas in female Sprague-Dawley rats given oral doses (Belpoggi et al., 1995, 1997, 1998). NYS DOH derived values ranging from 20 ug/L to 100 ug/L from dose-response data for cancers in F344 rats and CD-1 mice after inhalation exposures (Bird et al., 1997). Dourson and Felter (1997) have suggested that the absorption percentage for oral MTBE doses is nearly 100% whereas the absorption percentage for inhaled MTBE doses ranges from 40% to less than 100%. Thus, they estimated the ratio of absorption (percentage absorbed after inhalation/percentage absorbed after ingestion) to be between 0.4 and 1. Applying the lower (health-protective) end of this range (0.4) to the inhalation-based values of 20 ug/L to 100 ug/L yields values (corrected for differences in absorption between oral and inhaled doses) of 8 ug/L (0.4 x 20 ug/L) to 40 ug/L (0.4 x 100 ug/L). The value of 8 ug/L was based on the dose-response data for testicular tumors in male F344 rats after inhalation exposures. The values based on the leukemia/lymphoma data or the inhalation studies, however, may have greater uncertainty than the selected value when used to assess the oncogenic risks from low-level oral exposures to MTBE (HEI, 1996; Mennear, 1997; NSTC, 1996, 1997; US EPA, 1997).

NON-ONCOGENIC EFFECTS (702.5)

The limited data on the non-oncogenic effects of oral doses of MTBE in laboratory animals indicate that the organs/organ systems most sensitive to exposure include the kidneys, liver, blood, testes, and the gastrointestinal and nervous systems (ATSDR, 1996; Clary, 1997; US EPA, 1997, 1998). These preliminary conclusions were derived from gavage studies; drinking water studies were not found. Additional information on the effects of oral exposures on organs/organ systems, development, and reproduction is necessary before all the targets for oral exposures can be confidently identified.

There are no adequate studies on the non-oncogenic effects of chronic oral exposures to MTBE. In the only oral subchronic study of MTBE, rats were given gavage doses of MTBE of 0, 100, 300, 900, or 1,200 mg/kg/day for 90 consecutive days (Robinson et al., 1990). The

US EPA (1997) identified the lowest dose in the study (100 mg/kg/day) as a no-observed-effect level (NOEL), based on increased kidney weights. The US EPA did not consider the increased incidence of diarrhea in animals at all dose levels as an effect of MTBE exposures and indicated that it was dependent on the gavage dosing regime. However, diarrhea was also observed in rats given dermal doses (40 mg/kg) of MTBE (ATSDR, 1996). ATSDR (1996) identified 100 mg/kg/day as a lowest-observed-effect level (LOEL) for diarrhea. Other evidence of toxicity at 100 mg/kg/day included clinical chemistry findings. ATSDR (1996) identified 100 mg/kg/day as a LOEL for decreased serum blood-urea-nitrogen levels in males and females (significantly lower than levels in controls ($p \leq 0.05$) at $\geq$ 100 mg/kg/day) and elevated serum cholesterol levels in females (significantly higher than levels in controls ($p \leq 0.05$) at $\geq$ 100 mg/kg/day). There is also evidence of decreased serum creatinine levels in males at $\geq$ 100 mg/kg/day ($p \leq 0.05$). Thus, 100 mg/kg/day is considered a LOEL.

If an uncertainty factor of 3,000 is applied to the LOEL of 100 mg/kg/day, an acceptable daily intake of 0.033 mg/kg/day can be derived for MTBE 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 (diarrhea, without other signs of clinical toxicity, and changes in blood chemistry). 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 value of 0.23 mg/L (230 ug/L) is derived assuming a 70-kg adult drinks 2 liters of water per day and allowing 20% of the acceptable daily intake to come from drinking water (702.2(c) and 702.5(c)).

The US EPA (1998) has an inhalation reference concentration (conceptually equivalent to an oral reference dose) of 3 milligrams per cubic meter (mg/m^3) for MTBE. This value was based on systemic toxicity (kidney and liver effects) observed in rats exposed to MTBE in air for 24 months. The US EPA considers it protective of the developmental/reproductive effects of inhaled MTBE. It was derived using procedures consistent with those outlined in paragraphs (a) and (b) of 702.5. A 70-kg adult inhaling 20 m^3/day has a daily MTBE intake of 0.86 mg/kg/day at the reference concentration of 3 mg/m^3. Thus, a value of 6 mg/L (6,000 ug/L) is derived from the reference concentration using the procedure outlined in 702.2(c) and 702.5(c), allowing 20% of the daily intake at the reference concentration to come from drinking water (i.e., ((0.86 mg/kg/day x 70-kg body weight)/2 L/day) x 0.2). Assuming the ratio of absorption for MTBE after inhalational and oral exposures is 0.4 (as discussed in section on Oncogenic Effects), a value of 2.4 mg/L (2,400 ug/L) is derived from the reference concentration using the procedure outlined in 702.2(c) and 702.5(c), allowing 20% of the daily absorbed dose at the reference concentration to come from drinking water (702.5 (c)) (i.e., ((0.86 mg/kg/day x 0.4 x 70-kg body weight)/2 L/day) x 0.2).

CHEMICAL CORRELATION (702.7)

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

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 10 ug/L (based on oncogenic effects) and is the value selected as the water quality value for MTBE.

REFERENCES

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SEARCH STRATEGY

Toxline (1981 to August, 1994) was searched linking the CAS RN for MTBE with the keyword "toxicity". Medline and Toxline (1995 - February 1999) were searched using MTBE as the keyword.

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

1. References

Belpoggi, F., M. Soffritti, and C. Maltoni. 1995. Methyl-tertiary-butyl ether (MTBE) - A gasoline additive - Causes testicular and lymphohaematopoietic cancer in rats. Toxicol. Indust. Health. **11**:119-149

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

Oncogenic Effect	Testicular tumors in male Sprague-Dawley rats
Dose Regime	0, 250, or 1,000 mg/kg 4 days/week for 104 weeks
Doses	0, 143, or 571 mg/kg/day (e.g., 250 mg/kg x 4/7 = 143mg/kg/day)
Incidence*	3/26, 5/25, 11/32
Rat body weight	0.5 kg

* denominator is number of animals alive when first testicular tumor was detected

3. Derivation of Cancer Potency Factor

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

Rat daily dose	=	1.0 ug/kg/day (TOX_RISK (linearized multistage model) estimate of 95% lower bound on dose associated with a 1×10^{-6} incidences)**
Human daily dose	=	0.29 ug/kg/day = 1.0 ug/kg/day x $(0.5 \text{ kg}/70 \text{ kg})^{0.25}$
Cancer potency factor	=	1×10^{-6} risk level/1×10^{-6} dose (i.e., 0.29 ug/kg/day)
	=	3.4×10^{-6} per ug/kg/day = 3.4×10^{-3} per mg/kg/day

**using a linear extrapolation gives 1.1 ug/kg/day (i.e., 95% lower bound on dose (110,000 ug/kg/day) associated with a 0.1 incidence / 100,000)

4. Derivation of Ambient Water Quality Value

Water value = (0.29 ug/kg/day x 70 kg) / 2 L/day = 10 ug/L

New York State Department of Health
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