MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

TO: File for Ethyl *tertiary* butyl ether (CAS# 637-92-3)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: November 28, 2023

SUBJECT: Screening Level for Ethyl *tertiary* butyl ether (CAS# 637-92-3)

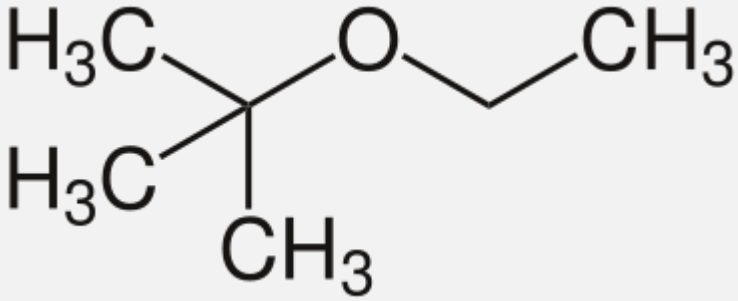
Summary

The initial risk screening level (IRSL) for ethyl *tertiary* butyl ether is 0.00001 µg/m^3 (annual averaging time) and the secondary screening level (SRSL) is 0.0001 µg/m^3 (annual averaging time).

Uses and Physical Chemical Properties

Ethyl *tertiary* butyl ether is used as an oxygenate gasoline additive to improve combustion efficiency and reduce pollutants in exhaust. "Ethyl *tertiary* butyl ether is released into the environment through gasoline leaks, evaporation, spills and other releases" (EPA, 2021).

Table 1. Physical/Chemical Properties of 1,1-Dichloroethylene

Structure	
CAS Number	637-92-3
Synonyms	Ethyl *t*-butyl ether; 2-ethoxy-2-methylpropane; ethyl *tert*-butyl ether; 2-methyl-2-ethoxypropane; ETBE
Appearance/Odor	Clear, light-yellow liquid with a strong, highly objectionable terpene-like odor and extremely flammable
Molecular Weight	102.177 g/mol
Melting Point	-94°C

Boiling Point	72.4°C
Flash Point	-19°C (closed cup)
Autoignition Temperature	375°C
Solubility: Water	$1.2 \times 10^{+4}$ mg/L at 20°C
Density	0.7364 g/cm^3 at 25°C
Vapor Pressure	124 mm Hg at 25°C
Henry's Law Constant	1.64×10^{-3} atm-m^3 /mole at 25°C

Literature Search

The literature was searched to find relevant data to assess the toxicity of ethyl *tertiary* butyl ether. The following references or databases were searched: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Levels (RELs), International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) SciFinder (searched 6/2/2023), U.S. EPA ChemView, California Office of Environmental Health Hazard Assessment (OEHHA), the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry (ATSDR), European Chemical Agency (ECHA), and the U.S. National Toxicology Program (NTP).

Key Study

The IRSL was based on the EPA IRIS inhalation unit risk (IUR) of 8×10^{-5} per mg/m^3. EPA Cancer Guidelines (EPA, 2005), "the evidence of carcinogenic potential for ETBE is *suggestive* for inhalation exposure but *inadequate* for oral exposure. ETBE induced liver tumors in male (but not female) rats in a 2-year inhalation exposure study (Saito et al., 2013; JPEC 2010)" (EPA, 2021). "In F344 rats, administration of ETBE via inhalation increased hepatocellular adenomas in males in an exposure-dependent manner, as indicated by a significant positive trend (p<0.001 with Peto's test). Hepatocellular tumors were not increased in female rats (Saito et al., 2013). A significantly increased incidence of hepatocellular adenomas or carcinomas (only one carcinoma observed) was observed at the highest dose tested in males, and three hepatocellular adenomas were observed at the two lower concentrations. Significant increases in preneoplastic foci (basophilic and eosinophilic foci) were also observed in male rats (Saito et al., 2013)" (EPA, 2021).

"A quantitative estimate of carcinogenic potential from inhalation exposure to ETBE was based on the increased incidence of hepatocellular adenomas and carcinomas in male F344 rats following 2-year inhalation exposure (Saito et al., 2013; JPEC 2010). The study included histological examinations for tumors in many different tissues, contained three exposure levels and controls, contained adequate numbers of animals per dose

group (~50/sex/group), treated the animals for up to 2 years, and included detailed reporting of methods and results" (EPA, 2021).

"…[S]upplementary evidence from two-stage initiation-promotion oral carcinogenesis bioassays indicate increased mutagen-initiated liver tumors, as well as increased tumor incidence in the thyroid, colon, and urinary bladder" (EPA, 2021).

There are also susceptible populations that may be more affected by exposure to ethyl *tertiary* butyl ether. "ETBE is metabolized to *tert*-butanol and acetaldehyde. Evidence is suggestive that genetic polymorphism of aldehyde dehydrogenase (ALDH) – the enzyme that oxidizes acetaldehyde to acetic acid – could affect ETBE toxicity. The virtually inactive form, ALDH2*2, is found in about one-half of all East Asians [and by extension people of East Asian ancestry; Brennan et al. (2004)]. Evidence is strong in humans that this ALDH2 variant increases the internal dose of acetaldehyde and the cancer risks from acetaldehyde, especially in the development of ethanol-related cancers (Eriksson, 2015; IARC, 2010). Several in vivo and in vitro genotoxicity assays in Aldh2 knockout (KO) and heterozygous mice reported that genotoxicity was significantly increased compared with wild-type controls following ETBE exposure to similar doses associated with cancer and noncancer effects in rodents (Weng et al., 2019; Weng et al., 2014; Weng et al., 2013; Weng et al., 2012; Weng et al., 2011). Inhalation ETBE exposure increased blood concentrations of acetaldehyde in Aldh2 KO mice compared with wild type (Weng et al., 2013). Thus, exposure to ETBE in individuals with the ALKH2*2 variant would be expected to increase the internal dose of acetaldehyde and potentially increase risks associated with acetaldehyde produced by ETBE metabolism in the liver. Collectively, these data present evidence that people with diminished ALDH2 activity could be considered a susceptible population that could be more sensitive to liver toxicity from ETBE exposure" (EPA, 2021).

"The available evidence base for the nuclear hormone receptor MOAs (i.e., peroxisome proliferator-activated receptor α [PPARα], pregnane X receptor [PxR], and the constitutive androstane receptor [CAR]) was inadequate to determine the role these pathways play, if any in ETBE-induced liver carcinogenesis" (EPA, 2021).

IRSL Derivation

"An inhalation unit risk was derived for liver tumors in male F344 rats. The modeled ETBE POD was scaled to an HEC according to EPA guidance based on inhalation dosimetry for a Category 3 gas (EPA, 1994). Using linear extrapolation from the benchmark concentration lower confidence level corresponding to 10% extra risk ($BMCL_{10}$), a human equivalent inhalation unit risk was derived using inhalation unit risk = $0.1/BMCL_{10}$ and calculated to be 8×10^{-5} per mg/m^3" (EPA, 2021). Converting EPA's IUR of 8×10^{-5} per mg/m^3 to $\mu g/m^3$ gives 0.08 per $\mu g/m^3$ which can be used to determine the initial risk screening level under Rule 231(1).

Rule 231(1) was used to develop the IRSL using the following equation:

$$IRSL = \frac{1 \times 10^{-6}}{Unit\ Risk}$$

Where:
Unit Risk = Additional lifetime cancer risk occurring in a population in which all individuals are exposed continuously for life to a concentration of 1 microgram per cubic meter of the chemical in the air. Using the EPA IUR value above in the IRSL equation:

$$IRSL = \frac{0.000001}{0.08\ (^{\mu g}/_{m^3})^{-1}} = 0.0000125\ ^{\mu g}/_{m^3} \approx 0.00001\ ^{\mu g}/_{m^3}$$

According to Rule 231(3) the averaging time for an IRSL or SRSL is annual. Therefore, the IRSL for ethyl *tertiary* butyl ether is 0.00001 µg/m^3 with an annual averaging time and the SRSL is 0.0001 µg/m^3 with an annual averaging time.

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