MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Ethyl alcohol (CAS # 64-17-5)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: Ethyl alcohol ITSL justification

DATE: February 9, 2017

The current ITSL for Ethyl alcohol is 19000 ug/m^3, with 1 hour averaging time (AT).

This ITSL was previously established on April 16, 1992 at 19000 ug/m^3 with 8 hr AT (see attached). The basis for that ITSL was the ACGIH occupational exposure limit (OEL) which was a TLV-TWA of 1000 ppm (1880 mg/m^3). In 2009, the ACGIH updated their OEL by establishing a TLV-Short Term Exposure Limit (STEL) at he same concentration, 1000 ppm (1880 mg/m^3). The ACGIH (2009) rationale was that the STEL is protective from respiratory and ocular irritation; the most critical effect is acute upper respiratory tract irritation. The TLV-STEL was recommended without a TLV-TWA because the respiratory and eye irritant effects occur well below concentrations that have been shown to cause long-term effects. ACGIH (2009) noted that ethanol can cause fetal alcohol syndrome from drinking alcoholic beverages, but that there is no evidence that industrial exposure to ethanol is a developmental toxicity hazard. Rats exposed by inhalation during gestation had maternal toxicity and malformations at 20,000 ppm (2%), but not at 10,000 ppm (1%) concentrations in the air (ACGIH, 2009).

The ITSL is derived in accordance with Rule 232(1)(c) as 1% of the OEL:

$$\text{ITSL} = \frac{1880\ \text{E+3 ug/m}^3}{100} = 18800\ \text{ug/m}^3 \sim 19000\ \text{ug/m}^3\ (1\text{ hour AT})$$

Reference:
ACGIH. 2009. Documentation of the TLVs and BEIs. Ethanol.

Michigan Department of Natural Resources

Interoffice Communication

April 16, 1992

To : Ethanol File

From : Gary Butterfield

Subject : AAC for Ethanol (CAS # 64-17-5)

Toxicity data for ethanol from the inhalation route of exposure is surprisingly scarce. The ACGIH has a TLV of 1000 ppm for ethanol based on, relatively old data of worker complaints (irritation to eyes and respiratory tract) when exposed to 1000 ppm, Browning (1956) and Lester & Greenberg (1951). This poorly characterized and quantified data appears to be the only human inhalation toxicity data available. In addition to the TLV, the results of animal studies following ethanol exposure indicate hazards from inhalation exposure do occur. Teratogenic effects were studied by Nelson et al (1985) who exposed pregnant rats to ethanol vapors at relatively high concentrations of 0, 10000, 16000 or 20000 ppm. Maternal toxicity was evident as narcosis and reduced food consumption at 20000 ppm. No pathological findings were reported. Male fetuses were found to have depressed body weights in both the 16000 and 20000 ppm groups. From this study, a NOAEL of 10000 ppm (or 19000 mg/m3) can be identified. In another reproductive type study, evidence of a lower NOAEL was presented by Nelson et al (1988). In this study, altered brain biochemical levels observed in offspring of adults exposed to 10000 ppm was used as evidence of adverse effects. The parental adults were exposed to 10000 or 16000 ppm ethanol for six weeks prior to mating to untreated adults. No evaluation of other organ effects, including liver effects - a known target organ - was reported in this study. At slightly lower exposure levels, Goldin and Wickramasinghe (1987) found continuous exposure for upto 19 days to approximately 13000 mg/m3 (or 6800 ppm) caused liver changes in mice, within two days. The changes after two days included fatty microvesiculation of hepatocytes. By the fourth day of exposure, midzonal and pericentral hepatocytes had fatty changes. After five days, scattered foci of inflammatory neutrophilic exudation and hepatocyte necrosis were present. These changes are consistent with liver pathology observed in livers during human alcoholism. Unfortunately, this study reported no details of individual animal pathology findings. Group results were reported in summary form. The number of animals per exposure group was also small and poorly described. Behavioral changes following inhalation exposure to ethanol were reported by Ghosh et al (1991a), who found altered effects on lever pressing in rats at exposure concentrations of only 100 ppm. Ghosh et al (1991b) also found effects on the sleep/wake cycle, indicative of an arousal action, at concentrations of 100 and 400 ppm. Inconsistent with a dose-response relationship, this study did not find those arousal

effects at higher ethanol concentrations.

Evidence of the rapid elimination of ethanol from blood by zero order kinetics was provided by Ferko and Bobyock (1979). There were no reports of absorption rates for various exposure routes found. However, it is anticipated that from either the oral or inhalation route of exposure absorption efficiency will be high. As the majority of human toxicity data is based on oral exposure and as both exposure routes are anticipated to have high absorption efficiency, it is feasible to calculate an AAC from oral data. Some problems that should be considered when using oral data include the following. The data on the amount of alcohol consumed in most of these studies is based on a response to a questionnaire or surveys - some question of accuracy may come into play as these amounts are dependent on recall ability, as well as, honesty. As with all epidemiology studies, the impacts from other exposures (smoking, socio-economic status, proper diet, etc) may also have had an influence on the pathology endpoint or symptoms and may not have been accounted for by the authors. Another consideration is the oral exposure route may cause high blood concentrations to be achieved over short time periods, thus averaging alcohol consumption from couple of drinks over a daily period may not be consistent with long inhalation periods.

The human fetus is known to be quite sensitive to alcohol exposure. The maternal dose of ethanol associated with Fetal Alcohol Syndrome is much lower than the ethanol dose associated with liver pathology in alcoholics. Therefore an AAC based on the NOAEL for fetal effects would be protective of the most sensitive time period for humans. Several authors have attempted to identify the amount of alcohol that can be consumed during pregnancy without affecting the fetus (ie. a NOAEL).

The highest NOAEL estimate came from Ernhart et al (1987) who was able to identify an increase in the cranio-facial abnormalities (a symptom that has been associated with Fetal Alcohol Syndrome or FAS) in mothers that consumed more than 3 oz of alcohol per day. The authors assumed a fixed amount of alcohol per drink, ie. 3 oz was assumed to be received from consumption of 6 drinks.

Many authors identified a NOAEL of 1 ounce of ethanol. Lumley et al (1985) reported a reduced birth body weight in young from mothers that consumed 2 or 3 drinks per day or more. The authors reported a NOAEL of 2 drinks per day based on their data. The specific amount of alcohol in those 2 drinks was not reported, however most authors used 0.5 ounce per drink. There was a discussion of why FAS was not reported. This seems to be related to specific examination procedures that need to be conducted in order to diagnose FAS. Those exams were not consistently performed in this study.

Other authors reporting similar exposure as the NOAEL included, Barr et al (1984) found a relationship between one or two drinks per day and reduced body weight and length at 8 months of age. Scher et al (1988) examined the neurophysiological effects (altered

sleep cycle and arousal) of maternal alcohol consumption. Mothers consuming more than one ounce per day had infants with neurophysiological effects. Hanson et al (1978) also used self reported alcohol use data to classify infant exposure. Consumption of more than 1 ounce of alcohol per day was associated with an increased number of children with features consistent with fetal alcohol syndrome. Tennes and Blackard (1980) found no relationship between consumption of 60 ounces per 90 days (or an average of 0.67 oz./d) and infant weight, length, or head circumference.

A few authors reported a NOAEL of slightly less than one ounce per day. In Day et al (1990), maternal alcohol consumption was classified as none, light (0 - 0.63 drinks/day), moderate (0.64 - 0.89 drinks /day) or heavy (> 0.89 drinks/day). Consumption of one drink per day was associated with reduced body weight and length at 8 months of age. This is a slightly lower dose than the NOAEL identified in the other studies. O'Connor et al (1986) found a relationship between maternal alcohol consumption and infant IQ scores. Moderate (0.1 to 1 ounce per day) and heavy (more than one ounce per day) consumption caused the reduced IQ scores.

In general, most of the authors seem to indicate consumption of more than one ounce per day (or two drinks) is the point where adverse effects are observed. Assuming a NOAEL of 1 ounce per day, the AAC of 330 ug/m3 (with annual averaging) as calculated below, would be consistent with the LOAEL of Goldin et al animal liver changes following inhalation.

from human oral data :
Assuming 100 % absorption from both inhalation and oral exposure, 62 kg female (for 18 to 35 year olds, EPA 1989 pg 5-5) breathing 20 m3 per day (a large inhalation rate range is possible, dependant on activity level and duration of time performing activity, EPA 1989 recommends a typical value of 20 m3/d, see pg 3-6), ethanol Spec Grav = 0.789 g/ml.
NOAEL : (1 oz x 29.57 ml/oz) x 0.789 g/ml = 23.3 g/d
assuming a 62 kg person, NOAEL = 0.376 g/kg.
if NOAEL for 1 oz/d is 0.376 g/kg then
AAC = (376 mg/kg)/(100) x (62 kg/20 m3) x (1/1) = 11.7 mg/m3
with annual averaging

TLV based AAC :
ACGIH TLV = 1000 ppm (1900 mg/m3) the AAC would be 19000 ug/m3 8 hr averaging

In conclusion, the poor quality of inhalation toxicity data for animals make identification of a NOAEL difficult, with little confidence the derived number. The human oral data clearly identify Fetal Alcohol Syndrome as the most sensitive of human effects. However, there is no human inhalation data on fetal effects from this route. The bolus effect from drinking alcohol with resultant

high short term blood concentrations, plus questionable self reporting of alcohol doses, makes use of this data of rather limited value for deriving an AAC. The use of one hundredth of the TLV for the AAC is considered the best available alternative at this time. From the one ounce per day alcohol consumption rate converted to an air concentration (see above), an AAC based on the TLV should be sufficiently protective for fetal effects. Therefore the AAC is 19 mg/m3 with an 8 hour average.

References:

ACGIH TLV

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