**MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY**

**INTEROFFICE COMMUNICATION**

TO: File for Propyl Alcohol (CAS # 71-23-8)

FROM: Keisha Williams, Air Quality Division

DATE: May 8, 2019

SUBJECT: Screening Level Update for Propyl Alcohol

The initial threshold screening level (ITSL) for propyl alcohol is 2500 µg/m$^3$ (8-hour averaging time) based on the Michigan Department of Environment, Great Lakes, and Energy* (EGLE), Air Quality Division (AQD) Rule 336.1232 (1)(c) and (2)(a). The chronic ITSL of 730 µg/m$^3$ (annual averaging time) is being rescinded at this time.

The following references or databases were searched to identify data to determine the screening level: United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), ChemView: the EPA's database on chemical health and safety data for chemicals subject to the Toxic Substances Control Act (TSCA), the TSCA documents in the National Technical Reports Library (NTRL) database, the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels, International Agency for Research on Cancer (IARC) Monographs, the American Chemical Society's SciFinder database, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Study Database, EPA Superfund Provisional Peer Reviewed Toxicity Values, EPA Acute Exposure Guideline Levels (AEGLs) for Airborne Chemicals, United States Department of Labor Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs), the Canadian Centre for Occupational Health and Safety's Registry of Toxic Effects of Chemical Substances (RTECS), the Toxnet databases: Hazardous Substances Data Bank and Toxline, Spacecraft Maximum Allowable Concentrations (SMACs), California Office of Environmental Health Hazard Assessments Reference Exposure Levels, Texas Commission on Environmental Quality (TCEQ) Effects Screening Levels (ESLs), German Maximale Arbeitsplatz-Konzentration (MAK) values, and European Chemicals Agency Registered Substances Dossiers.

## Background Information

Propyl alcohol, also known as n-propanol and 1-propanol, has been used as a solvent for several products including foods, inks, and pesticides (ACGIH, 2007; HSDB, 2001). It has also been used as an antiseptic, degreasing agent, and disinfectant. The chemical structure is provided in Figure 1 and chemical properties are listed in Table 1.

*Formerly the Michigan Department of Environmental Quality (MDEQ).

Figure 1. Chemical structure for propyl alcohol

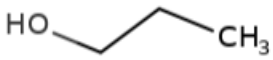


Table 1. Chemical and physical properties of propyl alcohol

| |
|---|
| Molecular weight: 60.096 grams/mole |
| Melting point: -127 °C |
| Boiling point: 97.2 °C |
| Vapor pressure: 21.0 mmHg at 25°C |
| Henrys Law Constant: 7.41e-06 atm-$m^3$/mole |
| Vapor density: 2.1, where air=1 |
| Physical state at standard temperature and pressure: liquid |
| Odor: mild, alcohol-like odor |
| Odor perception threshold: 0.07-100 mg/$m^3$ |

Reference: PubChem Compound Database

There are noted deficiencies in the toxicity database of propyl alcohol, especially the lack of chronic or subchronic studies (EPA, 1997; EPA, 2007; ECB, 2008). However, propyl alcohol is expected to have similar toxic effects as alcohols that have more extensive toxicity databases: isopropyl alcohol and ethanol. In general, inhalation of these toxic air contaminants may cause irritation, neurotoxicity, and developmental/reproductive toxicity (HSDB, 2001). Furthermore, these alcohols are all readily metabolized by alcohol dehydrogenase. However, subsequent metabolites, relative toxicity and respective critical effects can differ among these alcohols (Nelson et al., 1988; ACGIH, 2001; ACGIH, 2007; ACGIH, 2008; MDEQ, 2016, MDEQ, 2017). As a result, isopropyl alcohol and ethanol are described here for hazard identification.

Occupational exposure limits (OELs) are the main inhalation health benchmarks that have been derived for propyl alcohol specifically (ACGIH, 2007; NIOSH Pocket Guide; OSHA Chemical Database) (Table 2). The critical effects cited are narcosis and/or irritation (ACGIH, 2007; NIOSH Pocket Guide, OSHA Chemical Database). The health effects screening levels designed by the TCEQ are based on the ACGIH OELs (TCEQ, 2015). The EPA has determined that there is not enough information for derivation of a subchronic or chronic reference concentration (RfC) (EPA, 1997; EPA, 2007).

Table 2. Occupational Exposure Limits for Propyl Alcohol

| **Agency Reference** | **Benchmark Value for Agency-Specific Time Weighted Average OEL** |
|---|---|
| NIOSH | Reference effect levels (RELs)*: 500 mg/$m^3$ |
| ACGIH | Threshold limit value (TLV): 246 mg/$m^3$ |
| OSHA | Permissible exposure limit: 500 mg/$m^3$ |

* NOTE: Was also given a short-term exposure limit, 625 mg/$m^3$ and a skin notation

As compared to the OELs that were designed to be health-protective of narcosis and/or irritation, the developmental study in rats by Nelson et al., 1988 has been used to derive EGLE screening levels (EGLE Chemical Criteria Database), where the developmental effects of fetal skeletal malformations and decreased fetal body weight gain were observed.

**Key studies reviewed for ITSL derivation**

Because propyl alcohol is expected to be absorbed into the blood following inhalation exposure, portal of entry effects may not be the critical effects, and there are longer duration studies that have been conducted via oral administration as compared to inhalation exposure, the oral toxicity data were assessed. Risk assessments published by both the EPA and European Chemicals Bureau (ECB) in 2007 and 2008, respectively identified nearly the same oral, repeated dose studies where hepatotoxicity was identified as the critical effect (EPA, 2007; ECB, 2008). With this review, no other relevant oral studies were identified following the 2007 and 2008 evaluations.

Studies by Gibel et al. were identified as key studies to discuss here, because they are the only propyl alcohol-specific lifetime rodent studies (Gibel et al, 1974; Gibel et al., 1975). Furthermore, the Gibel et al. studies presented the lowest observable adverse effect level (LOAEL) identified out of the oral studies presented in the 2007 and 2008 evaluations. However, is it important to note that both the EPA and ECB concluded that the oral toxicity database was insufficient for health benchmark derivation. For the purposes of this evaluation, a potential ITSL based on the lifetime oral studies conducted by Gibel et al. will be further described.

These studies were published in German, but a translation is available through the National Technical Reports Library (EPA, 1992). In the Gibel et al. studies, 0.3 mL/kg propyl alcohol was given twice a week by gavage for a lifetime in male and female Wistar rats (EPA, 1992; EPA, 2007). Using a specific gravity of 0.804 grams/mL, this dose was estimated to be 241 mg/kg (EPA, 2007). Time matched controls were given a solution of 0.9% sodium chloride. While no malignant tumors were observed in the control group (N=25), 5 malignant tumors were observed in rats given propyl alcohol (N=18). More specifically, the 5 malignant tumors were "two myeloid leukemias, one liver-cell carcinoma, two liver sarcomas" (EPA, 1992). Furthermore, while 3 benign tumors were observed in the control group, 10 benign tumors were observed in the propyl alcohol group. It is unclear whether these tumors occurred in different animals or simultaneously in the same animal. Besides carcinogenicity, the Gibel et al. study reports, "…we must emphasize the severe toxic damage to the liver observed in almost all the animals, regardless of the nature of the alcohol, and also the hyperplasia of the hematopoetic parenchyma…Of n-propyl alcohol, we can speak of a hepato and hematoxic effect, as well as a carcinogenic one" (EPA, 1992). Taking the administered dose as the LOAEL for hepatoxicity and hemopoietic toxicity, a chronic ITSL can be derived as shown in Equation 1 pursuant to AQD Rule 336.1232 (1)(b) and (2)(b).

Equation 1.

$$ITSL = RfD\ x \frac{70kg}{20\ m^3}$$

$$\mathrm{RfD} = \frac{\mathrm{HED}}{\mathrm{UFs}}$$

$$\mathrm{HED} = \mathrm{POD_{adj}} x \frac{animal\ BW^{-0.25}}{human\ BW^{-0.25}}$$

$$\mathrm{POD_{adj}} = \mathrm{LOAEL\ x} \frac{\text{dose per week}}{\text{7 days per week}}$$

Where:

- $POD_{adj}$=time adjusted point of departure
- LOAEL=241 mg/kg
- Body weight of rat=0.3795 kg (MDEQ, 1996)
- Body weight of a person=70 kg
- UFs=uncertainty factors=10 for LOAEL to NOAEL extrapolation, 3 for interspecies extrapolation and 10 for intraspecies extrapolation

$$POD_{adj} = 241\frac{mg}{kg}\ per\ day\ x\frac{2\ doses\ given\ per\ week}{7\ days\ per\ week} = 68.85714286\frac{\text{mg}}{\text{kg}} per\ day$$

$$HED = 68.85714286\frac{mg}{kg} x\left(\frac{(0.3795\ kg)^{-.25}}{(70\ kg)^{-.25}}\right) = 250.5996601\frac{mg}{kg} per\ day$$

$$RfD = \frac{250.5996601\frac{mg}{kg} per\ day}{10x10x3} = 0.8353322\ x\frac{mg}{kg} per\ day$$

$$Potential\ ITSL = 0.8353322\ x\frac{mg}{kg} per\ day\ x\frac{70\ kg}{20\ m^3}\ x\frac{10^3(\mu g)}{mg} = 2923.662701\ \frac{\mu g}{m^3}$$
$$\approx 2900\ \frac{\mu g}{m^3}, annual\ averaging\ time$$

The Gibel et al. studies were the only studies found that looked at the carcinogenic effects of propyl alcohol over a lifetime of oral administration (EPA, 1992; EPA, 2007; ACGIH, 2007). However, there are major limitations with the study that prevent the use of these studies for initial risk screening level (IRSL) derivation, specifically only one treatment dose was used and the description of quantification of tumors in the individual rats in the dose group was not clearly presented. So, while EPA has classified propyl alcohol as a possible human carcinogen based on limited animal data, a cancer slope factor has not been derived. As a result, AQD will not regulate propyl alcohol with an IRSL at this time.

The ITSL established in 1992 was based on an inhalation study, where pregnant rats were exposed to 0, 3500, 7000 or 10000 ppm for 7 hours per day for 20 days during gestation (MDNR, 1992 [attached]; Nelson et al., 1988). The ITSL justification document further states, "Fetal skeletal malformations were increased, and fetal body weights were decreased in fetuses from dams exposed to 7000 and 10000 ppm. From this study a no observable adverse effect level (NOAEL) of 3500 ppm (or 8750 mg/m$^3$) can be identified". The ITSL was calculated as shown in Equation 1 pursuant to AQD Rule 336.1232 (1)(d).

Equation 1.

$$ITSL_{established\ in\ 1992} = \frac{NOAEL}{35\ x\ 100}\ x\frac{hours\ exposed}{24\ hours\ per\ day}$$

Where:

- NOAEL is 8750 mg/m$^3$
- Hours exposed were 7 hours per day
- Uncertainty factors (UFs) were 35 for 7 day duration study extrapolation to chronic duration, 10 for interspecies extrapolation, and 10 for intraspecies extrapolation

$$ITSL_{established\ in\ 1992} = \frac{8750\frac{mg}{m^3}}{35\ x\ 100}\ x\frac{7}{24} = 730\frac{\mu g}{m^3}, annual\ averaging\ time$$

Because the critical effect is a developmental effect, it is more appropriate to follow EPA guidance and recommendations on RfC derivation with consideration for developmental effects (EPA, 1991; EPA, 2002; EPA, 2012) as shown in Equation 2.

Equation 2.

$$ITSL = RfC_{based\ on\ developmental\ effects} = \frac{HEC}{UFs}$$

$$HEC = POD_{adj} x\ DAF$$

$$POD_{adj} = POD\ x\frac{hours\ of\ exposure}{7\ hours} = \ 8750\frac{mg}{m^3}\ x\frac{7}{24} = 2552.083\frac{mg}{m^3}$$

Where:

- $POD_{adj}$ is the time adjusted point of departure, where the NOAEL from the Nelson et al. (1988) study is used as the point of departure (POD).
- DAF= dosimetric adjustment factor for category 2 gas with systemic effects= default value=1
- UFs=uncertainty factors of 3 for interspecies differences and 10 for intraspecies differences

$$HEC = 2552.083\frac{mg}{m^3}\ x\ 1 = 2552.083\frac{mg}{m^3}$$

$$Potential\ ITSL = \frac{2552.083\frac{mg}{m^3}}{3\ x\ 10}x\frac{10^3\mu g}{mg} = 85,069.43\frac{\mu g}{m^3} \approx 85,000\ \frac{\mu g}{m^3}, 24\ hour\ averaging\ time$$

A summary of an inhalation study referenced from a 1992 report is available in the ECHA dossier for propyl alcohol (ECHA, 2018). In this study, groups of male and female rats were exposed to either 0, 100, 500 or 1000 ppm propyl alcohol for 6 hours per day for a total of 9 exposures on consecutive weekdays. The sample size was 15 rats per sex for the 0 and 1000 ppm groups, and 10 rats per sex for the 100 and 500 ppm groups. It was noted that perinasal and periocular encrustation was observed in 1 male in the group exposed to 500 ppm propyl alcohol. In the summary conclusion, it further notes “9 days of repeated inhalation exposures to n-propyl alcohol vapor produced only minimal clinical signs, most of which were observed only at the highest exposure concentration of 1000 ppm…Exposure-related clinical observations were limited to swollen periocular tissue, and perinasal and periocular encrustation in the 1000 ppm exposure concentration group.” The summary states that “no treatment-related systemic effects” were observed as measured by organ weight changes, body weight changes, urinalysis, hematology, evaluation for gross lesions during necropsy, and histopathology.

This study summary shows point of contact effects at concentrations below the NOAEL observed in the Nelson et al. studies. However, it is important to note that the clinical observations described above are characterized in the ECHA summary as the lowest observable effect concentration (LOEC), and not the LOAEL. The summary identified no critical effects, indicating that the local effects were determined to not be classifiable as “adverse.”

However, the local effects are dose-dependent effects that suggest point of contact effects are the critical effects if a high enough concentration is reached. Using 500 ppm as a NOAEL, potential ITSLs can be derived as shown in Equations 3 and 4 pursuant to AQD Rules 336.1232 (1) (d) and 336.1233 (1), respectively.

Equation 3.

$$Potential\ ITSL = \frac{NOAEL}{35\ x\ 100} x \frac{hours\ exposed\ per\ day}{24\ hours\ per\ day}$$

Where

- NOAEL=500 ppm or 500ppm x 0.0409 x 60.096 grams/mole=1228.9632 mg/$m^3$
- Hours exposed =6 hours per day
- UF of 20 is used instead of 35 for chronic extrapolation because the study is longer than 7 days.

$$Potential\ ITSL = \frac{1228.9632\ \frac{mg}{m^3}}{20\ x\ 100} x \frac{6\ hours}{24\ hours\ per\ day} x \frac{9\ days}{11\ days} x\ 1000 \frac{\mu g}{mg} = 125.6894182$$

$$\approx 126\ \frac{\mu g}{m^3}, annual\ averaging\ time$$

Equation 4.

$$Potential\ ITSL = \frac{\mathrm{POD}}{UF_h x\ UF_A x\ UF_L} x \frac{hours\ exposed}{AT}$$

Where:

- POD=point of departure=NOAEL =500 ppm or 1228.9632 mg/$m^3$
- Hours exposed =6 hours per day
- $UF_h$= uncertainty factor for average human to sensitive human extrapolation=10
- $UF_A$= uncertainty factor for animal to human extrapolation=10
- $UF_L$= uncertainty factor for LOAEL to NOAEL extrapolation=1

$$Potential\ ITSL = \frac{1228.9632\ \frac{mg}{m^3}}{10\ x\ 10} x \frac{6\ hours}{24\ hours\ per\ day} x\ 1000 \frac{\mu g}{mg} = 3072.408\ \frac{\mu g}{m^3}$$

$$Potential\ ITSL \approx 3000\ \frac{\mu g}{m^3}, 24\ hr\ averaging\ time$$

There are a number of limitations with using this study as the key study for ITSL derivation. While local effects were observed, these were not considered adverse and a LOAEL and NOAEL for local effects was not clearly described in the ECHA summary. As a result, using 500 ppm as the NOAEL is a judgement determination made here. The original research study, which may have more details about the experimental design and the results, could not be obtained. Because of this lack of information, this study will not be used for the final ITSL derivation.

The unadjusted TLV is expected to be health protective for developmental effects, because the TLV documentation states, “Based on comparisons of n-propanol studies in rats, Nelson et al. concluded that n-propanol was neither a selective developmental toxin nor would exposure to this material place human females at risk for alcohol-induced birth defects who are occupationally exposed at concentrations no greater than 200 ppm 8-hour TWA” (Nelson et al., 1990; ACGIH, 2007). While the derivation for the TLV itself is not known, the TLV support documentation further states that the TLV is “based on animal models of sensory irritation and on the structure activity relationship to 2-propanol” (ACGIH, 2007). This has been previously noted as a major limitation of the TLV, since it is based on acute toxicity data and a chemical structure comparison instead of a chemical-specific repeated study (MDNR, 1992). Especially considering the differences in relative potencies and critical effects, use of chemical structure comparisons without clear, detailed documentation of the rationale is a limitation of the TLV. However, protection against the acute effects seems most appropriate given the potential for portal of entry effects, irritancy, and developmental effects. A potential ITSL can be calculated from the TLV as shown in Equation 4 pursuant to AQD Rule 336.1232 (1)(c).

Equation 4.

$$ITSL = \frac{OEL}{100}$$

$$potential\ ITSL = \frac{246\frac{mg}{m^3}}{100} x \frac{10^3 \mu g}{mg} = 2{,}460\ \frac{\mu g}{m^3} \approx 2500\ \frac{\mu g}{m^3}, 8\ hour\ averaging\ time$$

Comparing the possible potential ITSLs, it may not be appropriate to derive an ITSL from an oral study since irritancy/point of contact effects seem to be the critical effects. Furthermore, based on the weight of evidence from potential ITSLs derived to be protective of local effects, these ITSLs would also be health-protective of potential systemic effects like developmental toxicity. Lastly, while there are limitations to all of the ITSLs based on local effects, an acute ITSL is more appropriate to protect against acute effects like irritation, and the ITSL based on the TLV is more appropriate to use as it is based on identified LOAEL and NOAEL information and has been evaluated multiple times by ACGIH.

**Therefore, the ITSL for propyl alcohol is 2500 µg/m$^3$, 8 hour averaging time.**

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**Michigan Department of Natural Resources**

**Interoffice Communication**

July 22, 1992

To : n-Propanol File (CAS # 71-23-8)

From : Gary Butterfield

Subject : ITSL for n-Propanol

The ACGIH has a TLV of 200 ppm (or 500 mg/m3) for n-propanol. However, it can be recommended that the ITSL not be derived from the TLV, as the TLV is based on acute toxicity data and a chemical structure comparison to other alcohols and their TLV, rather than an identified exposure level with no observed effects from a soundly conducted long term study. A question of confidence in an ITSL based on a TLV derived from such data could be raised.

Few toxicity studies evaluating n-propanol are available. One of the best of the available studies is Nelson et al (1988), who exposed pregnant rats to propanol vapors at concentrations of 0, 3500, 7000 or 10000 ppm during their gestation. Fetal skeletal malformations were increased, and fetal body weights were decreased in fetuses from dams exposed to 7000 and 10000 ppm. From this study a NOAEL of 3500 ppm (or 8750 mg/m3) can be identified. The route of exposure in this study, inhalation, is appropriate for use in development of an ITSL. Although exposure during gestation may be considered to be of a relatively short duration, when compared to lifetime studies, the NOAEL from this study will be used to derive the ITSL. Using the NOAEL from this study to derive the ITSL is appropriate because the NOAEL comes from a well conducted study of a sensitive life stage. The ITSL can be calculated as follows.

ITSL = (8750 mg/m3)/(35 x 100) x (7/24) = 730 ug/m3
with annual averaging

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