MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

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INTEROFFICE COMMUNICATION

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TO: File for Trimethyl propane triacrylate (CAS# 15625-89-5)

FROM: Keisha Williams, Air Quality Division

DATE: June 9, 2022

SUBJECT: Screening Level Derivation for Trimethyl Propane Triacrylate

The initial threshold screening levels for trimethyl propane triacrylate (TMPTA) are 1 µg/m^3 (annual averaging time) and 20 µg/m^3 (1-hour averaging time) based on the Michigan Department of Environment, Great Lakes, and Energy (EGLE) Air Quality Division (AQD) Rules 336.1232(1)(d) and (2)(c), and 336.1233(1) and (2).

The following references or databases were searched to identify data to determine the screening level: United States Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS), the Toxic Substances Control Act (TSCA) 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, Chemical Abstract Service (CAS) Online definition search, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Study Database, EGLE toxicology library, EPA Aggregated Computational Toxicology Resource (ACToR) Database, Chemical Safety Program Protective Action Criteria, EPA Superfund Provisional Peer Reviewed Toxicity Values, EPA Acute Exposure Guideline Levels (AEGLs) for Airborne Chemicals, EPA High Production Volume Database, 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), and European Chemicals Agency Registered Substances Dossiers.

Background Information

TMPTA (Figure 1) has been used to produce "ultraviolet-curable inks, electron beam irradiation-curable coatings, and polymers and resins; as a component of photopolymer and flexographic printing plates and photoresists; and as an ingredient in acrylic glues and anaerobic sealants" (HSDB, 2013). Chemical properties are listed in Table 1.

Figure 1. Chemical structure of TMPTA

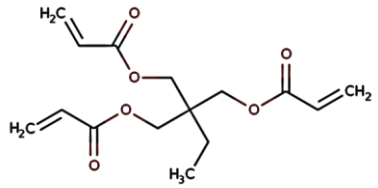


Table 1. Chemical properties of TMPTA

Molecular weight: 296.316 grams/mole
Boiling point: >200°C at 1 mmHg
Vapor pressure: 5.9 x 10^{-4} mmHg at 25°C (estimated)
Physical state at standard room temperature and pressure: liquid
Odor: acrylic/pungent

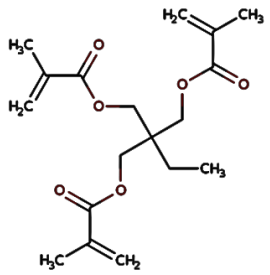
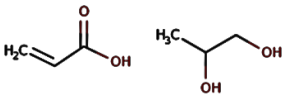
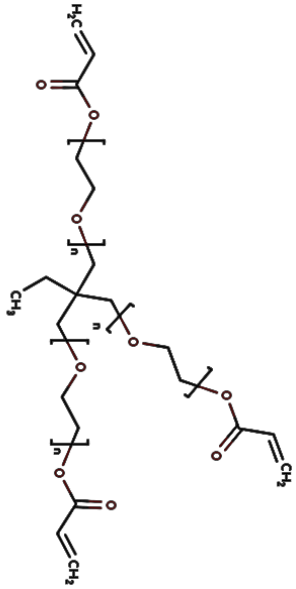
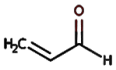
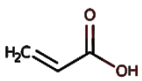
Reference: HSDB, 2013

The toxicity database for TMPTA is relatively limited, but other similar compounds have been more researched. Like other acrylates, TMPTA is a known skin sensitizer and a corrosive, irritating substance (Andrews and Clary, 1986; HSDB, 2013). In relation to this, portal of entry effects are often the critical effects with TMPTA exposure. Thus, route to route extrapolation was deemed inappropriate for this toxic air contaminant (TAC).

There have only been a few regulatory agencies that have derived health benchmarks for inhalation exposure to TMPTA. The American Industrial Hygiene Association has an occupational exposure limit of 1 mg/m^3, 8-hour averaging time, for TMPTA (AIHA, 2013). Based on this occupational exposure limit, TCEQ has derived a short-term ESL at 10 µg/m^3 and a long-term ESL at 1 µg/m^3 (TCEQ, 2010).

There are a few TACs with EGLE-derived screening levels that have similar chemical structures as TMPTA (See Table 2). As shown in Table 2, the critical effect identified for the associated ITSLs are often based on irritancy effects or upper respiratory injury. However, the basis also varies significantly depending on availability of chemical-specific information. Since TMPTA is expected to induce toxic effects similar to the critical effects identified for hydroxypropyl acrylate, acrolein, and acrylic acid, adoption of an ITSL from a similarly structured TAC may be appropriate here. However, preference will be given to developing an ITSL based on chemical-specific toxicity studies.

Table 2. Select TACs with similar chemical structures and moieties

Name (CAS#)	ITSL in µg/m^3, averaging time	Critical Effect	Chemical Structure	Reference
Trimethylolpropane trimethacrylate (3290-92-4)	20, annual	LD50		MDEQ, 1994
Hydroxypropyl acrylate (25584-83-2)	28, 8-hour	Irritancy and sensitizing effects		MDEQ, 2016
Triacrylate ester (28961-43-5)	0.1, annual	N/A; Default ITSL		MDEQ, 2002
Acrolein (107-02-8)	0.16, annual; 5, 1-hour	Nasal lesions (chronic effect) Irritation (acute effect)		MDEQ, 2008; MDEQ, 2013
Acrylic acid (79-10-7)	1, annual	Nasal epithelium degeneration		MDEQ, 2015

Evaluation of Cancer Risk

No carcinogenicity studies via inhalation exposure were identified for TMPTA. There are carcinogenicity studies via dermal application (NTP, 2005; NTP, 2012; Surh et al., 2014). These results show some TMPTA-induced carcinogenic potential with papillomas at the application site in one study, and liver and uterine tumors in another dermal study. Although these studies show TMPTA-induced carcinogenic potential with dermal application, it is unclear how applicable this is to the inhalation route of exposure. Furthermore, an inhalation unit risk cannot be derived based on the current data.

Mechanism of action to carcinogenicity has been investigated. In reviewing the genotoxicity data, some have determined that there is weak evidence for TMPTA-induced genotoxicity as there is a mix of negative and positive results from genotoxicity testing (NTP, 2012; Kirkland and Fowler, 2018; IARC, 2019; ECHA, 2021). Taken together, a clear mechanism of action has not been identified for TMPTA-induced carcinogenicity.

For the chemical family of acrylates, there has been a growing body of literature investigating the carcinogenicity of these TACs. Most pertinent to the inhalation-focused review performed here, animal studies have shown methyl acrylate-induced carcinogenicity via inhalation. The original study could not be obtained. However, a summary of the research is available (Wibbertmann et al., 2021). In the summary, it described that carcinogenicity was only observed at the highest dose. As a result, it would not be possible to develop an inhalation unit risk from this study. Furthermore, there are concerns that the highest dose may not be relevant to human exposure. Other animal studies did not show methyl methacrylate- or ethyl acrylate-induced carcinogenicity via inhalation (NTP, 1986; Miller, 1985). Based on lack of evidence showing carcinogenicity from acrylates via inhalation exposure and the lack of chemical-specific data, TMPTA will not be classified as a carcinogen via inhalation exposure at this time.

Review of relevant studies for noncarcinogen effects

Two unpublished inhalation toxicity studies were identified. These studies were conducted by Haskell Laboratory under contract from Dupont Chemical. Both are available in the National Technical Reports Library (EPA/OTS, 1992). One study determined the approximate lethal concentration (ALC) in young, male adult ChR-CD rats after 4 hours of exposure. The ALC was 0.0401 mg/L (40.1 mg/m^3), where 1 out of 6 rats died. TMPTA was categorized as “extremely toxic by inhalation.” Even at the lowest exposure concentration, 23.1 mg/m^3, “irregular respiration” was noted. The pathology notes further stated, “death at the highest dose [275 mg/m^3]…was probably due to tracheitis and obstruction of the tracheal lumen with proteinaceous exudate. A dose level of 0.0244 mg/L [24.4 mg/m^3] was tolerated apparently without adverse effects histologically…Histopathological examination of the test animals suggest that death at the highest level was due to severe irritation of the respiratory tract.”

In the second study, 6 rats were exposed for 4 hours per day for 5 days per week for 2 weeks to 5.7 $mg/m^3 \pm 1.5$ mg/m^3. Clinical signs were compared to those from time-matched controls. During the exposure period, rats showed irregular respiration, pilorection; restlessness; and face-pawing. One to two rats had nasal discharge, exhibited gasping; and continued to lose weight beginning at exposure 5. With a 2-week recovery period, exposed rats that experienced decrease weight gain resumed normal weight gain, and no histopathological changes were observed.

Using this 2-week study as the key study, a potential chronic ITSL can be derived pursuant to AQD Rule 232 (1)(d) as shown in Equation 1.

Equation 1. Potential chronic ITSL based on TMPTA-specific toxicity study

$$ITSL = \frac{LOAEL}{35\ x\ 100\ x\ UF} x \frac{hours\ exposed\ per\ day}{24\ hours\ per\ day}$$

Where:

-LOAEL is the lowest observable adverse effect level or lowest observable adverse effect concentration (LOAEC) at 5.7 mg/m^3

-35 is the duration extrapolation factor from a subacute study to a chronic study, 3.5 for subacute to subchronic extrapolation and 10 for subchronic to chronic extrapolation

-100 is the combined uncertainty factor for intraspecies variability (factor of 10) and interspecies extrapolation (factor of 10)

-UF is 3 for LOAEC to no observable adverse effect level for the reversible, critical effect of decreased weight gain

-Duration adjustments were made for the 4 hours per day, 5 days per week exposure

≈0.1 µg/m^3, annual averaging time (rounded to one significant figure)

Since there were acute clinical effects noted during the exposure in the subacute inhalation study, an acute ITSL can be derived as shown in Equation 2 pursuant to Rule 233. This is also supported by evidence on the category of acrylates, which are known to be portal of entry toxicants and sensory irritants (Fiume, 2002). Given that acrylates are known sensory irritants, adjustments for Haber's law will not be applied here.

Equation 2. Acute ITSL based on TMPTA-specific toxicity study

$$acute\ ITSL = \frac{POD}{UF_H\ x\ UF_A\ x\ UF_L}\ x \frac{hours\ exposed}{averaging\ time}$$

Where:

-POD = Point of Departure = human equivalent concentration of the LOAEL,

-LOAEL is 5.7 mg/m^3, and dosimetric adjustment factors for toxicokinetics could not be determined because of lack of information, so the full uncertainty factor of 10 was used for interspecies extrapolation

-UF_H = 10 for average human to sensitive human extrapolation

-UF_L = 10 for LOAEL to NOAEL extrapolation

-Hours exposed = 4 hours

-AT = Averaging to of 1, 8, or 24 hours

Since the chemical-specific toxicity information for TMPTA is relatively limited, potential ITSLs based on similar TACs with relatively larger toxicity databases will be discussed here.

No inhalation route experiments were found that identified TMPTA-metabolites. However, TMPTA has been shown to undergo hydrolysis or degradation to produce acrylic acid in liver homogenates and whole blood preparations (ECHA, 2019; ECHA, 2021), so acrylic acid related ITSLs are particularly relevant to consider. Other potential metabolites include trimethylol-propane diacrylate, trimethylolpropane monoacrylate, and trimethylolpropane (ECHA, 2019). However, there are currently no SLs for these other TACs.

There also currently is not an acute ITSL for acrylic acid with which to compare the TMPTA-derived acute ITSL. However, the chronic ITSL for acrylic acid is:

- Derived from the EPA reference concentration for acrylic acid, where the key study is a 13-week, subchronic inhalation study in both genders and in two different animal species, and the critical effect is the portal of entry effect of nasal olfactory epithelium degeneration in mice at 5 ppm (14.94 mg/m^3) (USEPA, 1994).

- Supported by additional studies, including developmental studies and a two-generation reproductive study that support the use of the portal of entry effect as the critical effect, and a subacute study and acute studies that show a duration-response relationship where "there is an increase in incidence of response" with increasing exposure duration.

Given the chemical structure, 1 mole of TMPTA may produce 3 moles of acrylic acid. An ITSL for TMPTA based on the molecular weight adjustment of the chronic ITSL for acrylic acid is shown in Equation 3.

Equation 3. Chronic ITSL based on molecular weight adjustment of acrylic acid ITSL

$$Potential\ ITSL_{TMPTA} = ITSL_{acrylic\ acid} x\ TMPTA_{molecular\ weight\ adjustment\ factor}$$

Where:

$$Potential\ ITSL_{TMPTA} = 1 \frac{\mu g}{m^3}\ x\ \frac{296.316 \frac{grams}{mole} x\ 1\ mole}{\frac{72.0626\ grams}{mole} x\ 3\ moles} = 1.37064 \frac{\mu g}{m^3}$$

$$\approx 1 \frac{\mu g}{m^3}, annual\ averaging\ time$$

Since TMPTA is expected to convert to acrylic acid in the body and there is more confidence in the acrylic acid toxicity database, the chronic ITSL derived from acrylic acid ITSL will be used at this time.

Therefore, the chronic ITSL for TMPTA is 1 µg/m^3, annual averaging time and the acute ITSL is 20 µg/m^3, 1-hour averaging time.

References

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

Andrews, L. S., and Clary, J. J. 1986. Review of the toxicity of multifunctional acrylates. Journal of Toxicology and Environmental Health, Part A Current Issues, 19(2), 149-164.

ECHA. 2019. CLH report: Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: 2-ethyl-2-[[(1-oxoallyl)oxy]methyl]-1,3-propanediyl diacrylate; 2,2-bis(acryloyloxymethyl)butyl acrylate; trimethylolpropane triacrylate. Accessed June 1, 2022.

ECHA. 2021. Registration Dossier for 2-ethyl-2-[[(1-oxoallyl)oxy]methyl]-1,3-propanediyl diacrylate; 2,2-bis(acryloyloxymethyl)butyl acrylate; trimethylolpropane triacrylate (CAS No. 15625-89-5). Published in accordance with the Registration, Evaluation, Authorisation and Restriction of Chemicals (i.e., REACH) legislation. Accessed April 23, 2021. https://echa.europa.eu/registration-dossier/-/registered-dossier/15232

EPA/OTS. 1992. Initial Submission: Acute Inhalation and Subacute Inhalation Toxicity of 1,3-propanediol, 2-ethyl-2-(hydroxymethyl), Triacrylate in Rats with Cover Letter Dated 101592. U.S. EPA Fiche #: OTS0571328.

EPA. 2012. Advances In Inhalation Gas Dosimetry For Derivation of A Reference Concentration (RfC) and Use In Risk Assessment. U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-12/044.

Fiume, M. Z. 2002. Final report on the safety assessment of acrylates copolymer and 33 related cosmetic ingredients. International journal of toxicology, 21, 1-50.

HSDB [Internet]. 2013. Bethesda (MD): National Library of Medicine (US); [Last Revision Date September 4, 2013; cited on March 6, 2019]. Trimethylolpropane triacrylate; Hazardous Substances Databank Number: 8054. Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+8054

IARC [Internet]. 2018. List of Classifications, Volumes 1-123. Accessed from International Agency for Research on Cancer website on March 6, 2019. https://monographs.iarc.fr/list-of-classifications-volumes/

IARC. 2019. Isobutyl Nitrite, β-Picoline, and Some Acrylates. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans.

Kirkland, D. and Fowler, P. 2018. A review of the genotoxicity of trimethylolpropane triacrylate (TMPTA). Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 828, 36-45.

MDEQ. 1994. *Memo from Gary Butterfield to File for Trimethylolpropane trimethacrylate (3290-92-4).* January 5, 1994. Michigan Department Environmental Quality, Air Quality Division.
MDEQ. 2002. *Memo from Marco Bianchi to File for Triacrylate ester (28961-43-5).* September 24, 2002. Michigan Department Environmental Quality, Air Quality Division.

MDEQ. 2008. *Memo from Catherine Simon to File for Acrolein (107-02-8).* January 11, 2008. Michigan Department Environmental Quality, Air Quality Division.

MDEQ. 2013. *Memo from Michael Depa to File for Acrolein (107-02-8).* June 14, 2013. Michigan Department Environmental Quality, Air Quality Division.

MDEQ. 2015. *Memo from Robert Sills to File for Acrylic Acid (79-10-7).* October 30, 2015. Michigan Department Environmental Quality, Air Quality Division.

MDEQ. 2016. *Memo from Mike Depa to File for Hydroxypropyl acrylate (Acrylic acid, Monoester with Propane-1,2, - Diol) (25584-83-2).* June 6, 2016. Michigan Department Environmental Quality, Air Quality Division.

Miller, R. R., Young, J. T., Kociba, R. J., Keyes, D. G., Bodner, K. M., Calhoun, L. L., Ayres, J. A. 1985. Chronic toxicity and oncogenicity bioassay of inhaled ethyl acrylate in Fischer 344 rats and B6C3F1 mice. Drug and chemical toxicology, 8(1-2), 1-42.

NTP. 2005. Toxicology studies of trimethylolpropane triacrylate (technical grade) (CAS No. 15625-89-5) in F344/N rats, B6C3F1 mice, and genetically modified (FVB Tg. AC hemizygous) mice (dermal studies). National Toxicology Program genetically modified model report, (3), 1.

NTP. 2012. Toxicology and carcinogenesis studies of trimethylolpropane triacrylate (technical grade) (CASRN 15625-89-5) in F344/N rats and B6C3F1/N mice (dermal studies). National Toxicology Program technical report series, (576), 1.

Surh, I., Rao, D. B., Cesta, M. F., Hébert, C. D., Mann, J. F., Cunny, H., Kissling, G.E., David Malarkey, D., and Chhabra, R. S. 2014. Species and gender differences in the carcinogenic activity of trimethylolpropane triacrylate in rats and mice. Food and Chemical Toxicology, 66, 254-261.

TCEQ. 2010. Tox ESL-Summary Report for Trimethylolpropane Triacrylate. Accessed from the Texas Air Monitoring Information web interface on March 6, 2019. https://www17.tceq.texas.gov/tamis/index.cfm?fuseaction=report.main

USEPA. 1994. IRIS database. Acrylic Acid (CASRN 79-10-7) Chemical Assessment Summary. Accessed on May 19, 2022. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0002_summary.pdf#nameddest=rfc%20htm

Wibbertmann, A., Bitsch, A., & Kuper, C. F. 2021. Comprehensive analysis of chronic rodent inhalation toxicity studies for methyl acrylate with attention to test conditions exceeding a maximum tolerated concentration. Regulatory Toxicology and Pharmacology, 104900.

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