MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

June 6, 2016

TO: Hydroxypropyl Acrylate (Acrylic Acid, Monoester with Propane-1,2,-Diol) (CAS No. 25584-83-2)

FROM: Mike Depa, Toxics Unit, Air Quality Division

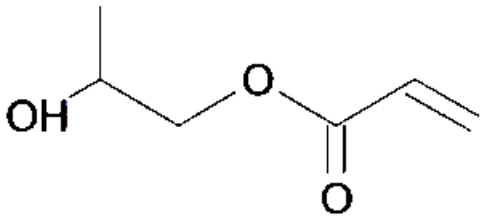
SUBJECT: Initial Threshold Screening Level

The Initial Threshold Screening Level (ITSL) for hydroxypropyl acrylate is 28 µg/m^3, with 8-hr averaging time.

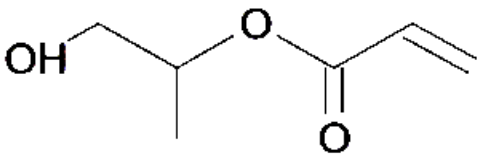
Hydroxypropyl acrylate (HPA)(25584-83-2) is a mixture of two isomers; see below. A typical commercial sample of hydroxypropyl acrylate contains approximately 75-80% 2-hydroxypropyl acrylate and 20-25% 1-methyl-2-hydroxyethyl acrylate (SIDS, 2005).

Molar mass = 130.1 kg/kmol
Vapor pressure at 20 °C = 0.1 mbar
Melting point = 23.4 °C
Boiling point = 198.5 °C

Figure 1. Isomers of Hydroxypropyl Acrylate (25584-83-2)



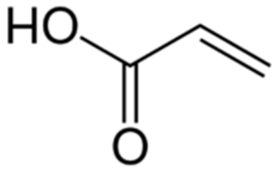
2-hydroxypropyl acrylate (75-80%)
CAS Number: 999-61-1



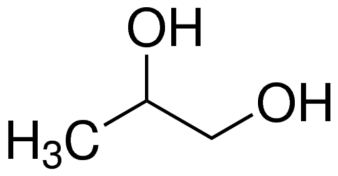
2-hydroxy-1-methylethyl acrylate (20-25%)
CAS Number: 2918-23-2

A similar compound, hydroxy***ethyl*** acrylate, is rapidly metabolized via hydrolysis via the ester functional group into acrylic acid and 1,2-ethanediol. Based on the similarity of hydroxypropyl acrylate to HPA, it is expected that HPA would metabolize rapidly into acrylic acid and 1,2-propanediol (see below). This is the same conclusion that was reached by the International Program on Chemical Safety (IPCS) and Canadian Centre for Occupational Health and Safety (CCOHS)(SIDS, 2005).

Figure 2. Ester Cleavage Products of Hydroxypropyl Acrylate



Acrylic Acid (79-10-7)
ITSL = 1 µg/m³ annual



1,2-Propanediol (57-55-6)

Hydroxypropyl acrylate is photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of 7.4 hours (SIDS, 2005). The hydrolysis rate of HPA is pH dependent with hydrolysis halflives of >490 days and >230 days at pH 3 and pH 7, respectively (SIDS, 2005). The hydrolysis half-life at pH 11 is 0.056 days (approximately 1 hr 21 minutes)(SIDS, 2005).

Animal Toxicity Information

A 1-month inhalation study was performed (ECHA, 2016). Three groups of animals, each consisting of 2 male beagle dogs, 4 male New Zealand white rabbits, 10 male Sprague-Dawley rats (Spartan strain) and 20 Swiss-Webster male mice were used in this study. Two groups of animals were designated to be exposed to HPA vapours of 5 ppm (0.027 mg/L) or 10 ppm (0.053 mg/L), respectively. The duration of exposure was 6 hours per day, 5 days per week for a total of 20 exposures for dogs and rabbits and 21 exposures for rats and mice in 30-31 days. The third group served as an unexposed control group.

Results of 28-day Inhalation Study (ECHA, 2016):

CLINICAL SIGNS AND MORTALITY

In the dog study, no mortality was observed. During the exposures, both dogs exposed to 10 ppm exhibited nasal irritation (exudative rhinitis) and eye irritation (bilateral corneal cloudiness, slight corneal edema, and bilateral suppurative conjunctivitis). One dog exposed to 5 ppm exhibited exudative rhinitis approximately half way through the study.

BODY WEIGHT AND WEIGHT GAIN

During the exposures, both dogs exposed to 10 ppm lost body weight (from 2 to 10 %). The body weights showed some recovery during the weekends when no exposures occurred. The dogs exposed to 5 ppm HPA showed no significant difference in body weight changes from the control dogs.

HEMATOLOGY

No treatment-related effects on the hematological measurements, red cell counts, white cell counts, differential white cell counts, hemoglobin concentration, and packed cell volume were identified.

CLINICAL CHEMISTRY

No treatment-related effects on the clinical chemistry measurements, BUN, blood glucose, SGPT, SGOT, and alkaline phosphatase were found.

URINALYSIS

No treatment-related effects on the urinalysis parameters, specific gravity, pH, glucose, protein, and the presence or absence of ketones, bilirubin and blood were noted. Microscopic examination of urine sediment revealed no abnormal numbers of blood cells, casts, or bacteria.

ORGAN WEIGHTS

The absolute and relative organ weights were not affected by treatment with the substance vapour.

GROSS PATHOLOGY
At necropsy, gross pathologic changes related to exposure were found in the upper respiratory system of all exposed dogs as well as the trachea and lungs of the 10 ppm HPA group of dogs. These gross changes were characterized by exudative rhinitis, tracheitis, and suppurative bronchopneumonia. One dog of the 10 ppm group exhibited bilateral keratitis. Three of the four exposed dogs had small-sized prostates and, in one of the dogs exposed to 5 ppm HPA, the testes also appeared hypoplastic. These changes were suggestive of sexual immaturity and not considered a primary effect of exposure.

HISTOPATHOLOGY: NON-NEOPLASTIC
Microscopic examination of the tissues revealed a marked inflammatory reaction in the upper respiratory system of all exposed dogs. Microscopic lesions included bilateral suppurative rhinitis, squamous metaplasia and hyperplasia of the lining epithelium with focal area of ulceration in the nasal turbinate mucosa. These lesions extended to the trachea and lungs of the high exposure group resulting in bronchopneumonia. No tracheal changes were present in the two dogs exposed to 5 ppm. However, focal foreign body pneumonia resulting from aspirated food particles was present in one dog from each exposure group, and was interpreted to be secondary to the upper respiratory irritation. In addition, dogs exposed to 10 ppm HPA had pneumonic changes in the lung as a result of the inhalation exposure to vapours of HPA. One high exposure level dog showed bilateral subacute keratitis and conjunctivitis considered related to exposure. Microscopic testicular changes in three of the four exposed dogs were characterized by occasional seminiferous tubules showing decreased spermatogenic activity. Individual seminiferous tubules in these testes infrequently contained giant cell formation suggestive of a degenerative change; however, sexual immaturity was considered the most plausible interpretation. One of the high exposure level dogs did not show microscopic testicular changes. The gross and microscopic changes in the testes and prostate were considered to be secondary to the stress associated with the respiratory system involvement and the sexual immaturity of these dogs. In the same dog of the high dose level with the most severe involvement of the respiratory system and the testicular changes, there was a generalized decrease in lymphoid and thymic cellular elements. This was also interpreted to be a secondary stress response.
Concentrations used throughout the report were referred to as 5 and 10 ppm (which corresponded to 0.027 and 0.053 mg/L air, respectively), the approximate values for the average analytical concentrations.

CONCLUSION
Dogs were the most sensitive species among the four species tested (dogs, rabbits, rats, mice). At 0.027 and 0.053 mg/L of exposure the upper and lower respiratory tract was the main target. The upper respiratory tract showed a marked inflammatory reaction which extended into the lower respiratory tract. The toxicity on the respiratory tract caused some stress-mediated secondary effects on body weight, thymus, lymphoid tissues and reproductive organs. (ECHA, 2016)

Derivation of a Potential ITSL

A potential ITSL can be derived from the 28-day Inhalation Study (ECHA, 2016) summarized above. Rule 232(1)(d) provides an equation where the lowest-observed-adverse-effect-level (LOAEL) of 0.027 mg/L is used. Note that 27 mg/m^3 is used in the 232(1)(d) equation below, which is equivalent to 0.027 mg/L using the unit relationship of 1000L per m^3.

$$ITSL = LOAEL/(35 \times 100 \times UF) \times (\text{hours exposed per day})/(24 \text{ hrs})$$

Where, the Uncertainty Factor, or UF, is a value from 1 to 10 determined on a case-by-case basis, considering type and severity of effect. Because the effects observed in the lungs were described as “marked inflammatory reaction”, a full 10-fold UF is justified. However, because the equation is for a 7 day study, whereas the study to be used is a 28-day study, the 35-fold factor in Rule 232(1)(d) is reduced to 20. The revised equation is shown as:

Potential ITSL = LOAEL/(20 x 100 x 10) x (hours exposed per day)/(24 hrs)

Potential ITSL = (27 mg/m³)/(20 x 100 x 10) x (6 hrs)/(24 hrs) x 1000µg/mg

Potential ITSL = 0.34 µg/m³; annual averaging time, pursuant to Rule 232(2)(c)

The developmental toxicity of HPA was evaluated in Sprague-Dawley rats after inhalation exposure for 6 hours/day, on gestation days 6 to 20 (Saillenfait et al., 1999). The exposure concentrations were 0, 1, 5, or 10 ppm (0, 5.3, 27, or 53 mg/m³). Dose groups consisted of 20 to 22 pregnant rats. Maternal body weights were lower than control for the 10 ppm group and weight gain was reduced for the 5 and 10 ppm groups. There was no significant difference in the numbers of implantation sites and live fetuses, in the incidence of non-live implants and resorptions, or in the fetal sex ratio, or fetal body weight between control and treated animals. No treatment related increase in embryo/fetal lethality or fetal malformations was observed at any dose level. The incidence of external, visceral, and skeletal variations was similar to controls. The NOAECs were 1 ppm (5.3 mg/m³) for maternal toxicity and >10 ppm (53 mg/m³) for embryo-fetal toxicity and teratogenicity. This study was not used to derive a potential ITSL because the investigation of maternal toxic was limited to body weights and few other parameters that are necessary for a complete toxicological assessment.

Occupational Exposure Limit

The American Conference of Governmental and Industrial Hygienists (ACGIH) derived a Threshold Limit Value (TLV) for 2-hydroxypropyl acrylate in 1999 of 0.5 ppm (2.8 mg/m³)(ACGIH, 2014). The TLV for 2-hydroxypropyl acrylate specifically indicates that the TLV also applies to the mixture of HPA (CAS Number 25584-83-2). The ACGIH (2014) summarized the 28-day (21 exposure day) inhalation study as reported by ECHA (2016)(see above for summary). The TLV was set in order to minimize the potential for eye, nasal, and upper respiratory tract irritation (ACGIH, 2014). However, ACGIH (2014) does not describe substantial human dose-response data; instead relying primarily on animal data while designation this substance as a skin sensitizer.

Pursuant to Rule 232 hierarchy, a potential ITSL was derived as follows from Rule 232(1)(c):

ITSL = OEL/(100)

Where OEL is the occupational exposure limit is the ACGIH TLV of 2.8 mg/m³.

Potential ITSL = 2.8 mg/m³/100 x 1000µg/mg
Potential ITSL = 28 µg/m³; 8-hr averaging time, pursuant to Rule 232(2)(a)

The final ITSL is set at 28 µg/m³ with 8-hr averaging time based on the ACGIH TLV-TWA. Although the ECHA (2016) report indicates that dogs are a relatively sensitive species to irritancy effect, and that key study could support a duration adjusted LOAEL of 6750 µg/m³ (27 mg/m³ x 6hr/24hr x 1000µg/mg) and a potential ITSL of 0.34 µg/m³ with annual averaging time, the chosen ITSL better ensures protection from short-term peak exposures over 8 hours and potential irritancy and sensitization effects.

References

ACGIH. 2014. 2-Hydroxypropyl Acrylate (CAS Numbers 999-61-1 and 25584-83-2). Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices. Cincinnati OH. American Conference of Governmental Industrial Hygienists (ACGIH®)

ECHA. 2016. Acrylic acid, monoester with propane-1,2-diol (EC Number 247-118-0)(CAS Number 25584-83-2). Online Database. European Chemicals Agency Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland. <Seach in the CAS number field using “25584-83-2”> <Accessed 6-6-16> http://echa.europa.eu/information-on-chemicals/registered-substances

Saillenfait A, P Bonnet, F Gallissot, J C Protois, A Peltier and J F Fabriès (1999) Relative Developmental Toxicities of Acrylates in Rats Following Inhalation Exposure. Toxicological Sciences 48: 240-245.

SIDS. 2005. Hydroxypropyl Acrylate (CAS No. 25584-83-2). Screening Information Data Set (SIDS) for High Production Volume (HPV) Chemicals. INCHEM is a cooperative database produced by International Program on Chemical Safety (IPCS) and Canadian Centre for Occupational Health and Safety (CCOHS). Published by the United Nations Environment Programme (UNEP), UNEP Publications. SIDS Initial Assessment Report (SIAR). For SIDS Initial Assessment Meeting (SIAM) 20 Paris, France, 19-22 April, 2005. http://www.inchem.org/documents/sids/sids/25584832.pdf