MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

_____

INTEROFFICE COMMUNICATION

_____

February 3, 2017

TO: File for 2-Hydroxyethyl Acrylate (CAS No. 818-61-1)

FROM: Mike Depa, Air Quality Division, Toxics Unit

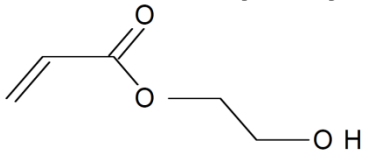
SUBJECT: Initial Threshold Screening Level

The Initial Threshold Screening Level (ITSL) 2-hydroxyethyl acrylate is 1 µg/m³ with annual averaging time.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), the National Institute of Occupational Safety and Health (NIOSH), the Agency for Toxic Substances and Disease Registry (ATSDR), the California Office of Environmental Health Hazard Assessment (Cal OEHHA), National Library of Medicine's TOXNET and TOXLINE, Toxic Substance Control Act (TSCA) Test Submissions (TSCATS), EPA's Provisional Peer Reviewed Toxicity Values for Superfund (PPRTV), European Chemicals Agency (ECHA) Risk Assessment (REACH) database, Chemical Abstract Service (CAS) SciFinder database and US EPA (epa.gov).

IUPAC Name: 2-hydroxyethylester 2-Propenoic acid (synonym ethylene glycol acrylate), Molecular weight is 116.12g. Molecular Formula: C5H8O3. The melting point is -60.2℃ and the boiling point is 210℃. Th e vapor pressure is 0.06974 hPa at 25℃. The measured log Kow has been reported to be -0.21. Hydroxyethyl acrylate is miscible in water at 25℃. The specific gravity is 1.101 g/cm^3 at 25℃.

Figure 1. Molecular Structure of Hydroxyethyl Acrylate (HEA)



Hydroxyethyl acrylate (HEA) is able to be broken down in the atmosphere by photodegradation. HEA is estimated to have an atmospheric half-life of 10 hours

based on its reaction rate with hydroxyl radicals. Based on its UV absorption spectrum it may also directly photolyze (Brun et al., 1976)

Dow Chemical is reported to have an occupational exposure limit (OEL) of 1 ppm (4.7 mg/m³) for 8-hr time-weighted-average (TWA) (UNEP, 2005). Sweden adopted an 8-hr TWA (time-weighted average concentration during an 8-h working period) of 1 ppm (~5 mg/m^3) and a STEL (short-term exposure limit during 15 min) of 2 ppm (~10 mg/m^3), with a skin notation and a note "sensitizer" (UNEP, 2005). In the Netherlands, the maximum acceptable concentration expressed as 8-h TWA is 0.05 ppm (0.24 mg/m^3) (UNEP, 2005). A search of the literature did not locate text or explanation of how these OELs were derived; therefore, they were not used to calculate a screening level.

Summary of Animal Toxics Studies

In a 4-week inhalation study 15 to 20 male rats per group were exposed for 7 hours/day, 5 days/week to HEA vapors at concentrations of 0, 5, 10 or 25 ppm (23.7, 47.4 or 118.5 mg/m^3) (Leong and Trice, 1970). Interim sacrifices were performed on the 5 and 10 ppm groups after 2 weeks of exposure. All animals were subjected to a gross and microscopic examination irrespective of whether they died during the treatment or were killed at the termination of treatment. There were two deaths during the 13-week study.

Histopathological examination in the 4-week study found ulcerative keratitis (superficial loss of cornea with inflammation) in all groups exposed to HEA. The incidence of this effect increased with the exposure concentration with the lesion occurring in 14, 6 and 3 animals in the 25, 10 and 5 ppm treatment groups respectively. Focal ulcerative rhinitis (superficial loss of nasal epithelial tissue with inflammation) was observed in 7 and 4 rats in the 25 and 10 ppm treatment groups, respectively, but was not seen in the control rats. Clinical signs of nasal irritation were observed at 10 ppm and 25 ppm produced dyspnea (shortness of breath) and abdominal bloating which became more severe as the number of exposures increased. There were 17 spontaneous deaths in the 25 ppm treatment group. Unfortunately because of the high incidence of chronic murine pneumonia in all groups (not treatment-related) it was impossible to characterize any lung pathology which might have been caused by exposure to HEA. At termination, mean body weights of rats exposed to 10 ppm for 20 days were significantly lower than controls. Relative weights of livers were higher for rats that were exposed to 10 and 5 ppm, relative kidney weight was increased at 10 ppm only. Testicular atrophy was observed histopathologically in one of 9 rats exposed to 10 ppm HEA for 20 exposures but was judged not to be treatment-related. No testicular atrophy was found in the highest exposure group. The lowest observed adverse effect concentration (LOAEC), based on corneal irritation, was 5 ppm (23.7 mg/m³)(Leong and Trice, 1970).

In a chronic inhalation study male and female Sprague-Dawley rats (99 or 100 animals per sex per dose group) were exposed to HEA 6 hours per day, 5 days/week

for 18 months at concentrations of 0.5 ppm (2.4 mg/m^3) or 5 ppm (24 mg/m^3)(Kociba et al., 1979). The control group consisting of 100 animals of each sex was exposed to air. After termination of treatment the male and female animals were left for a recovery period of 5 and 6 months respectively before being killed for examination post mortem. The study included a 12-month interim kill for pathological and cytogenetic examination. Histopathological examination was carried out for the following tissues of the control and 5 ppm groups, at interim and terminal sacrifice: brain, heart, liver kidneys, testes, lungs, thoracic and/or mesenteric lymph nodes, salivary glands, pancreas, adrenals, spleen, thymus, aorta, skeletal muscle, small intestine, large intestine, thyroid gland, trachea, spinal cord, peripheral nerve, pituitary gland, epididymides, urinary bladder, accessory sex glands, adipose tissue, ovaries, uterus, nasal turbinates, and any gross lesion suggestive of a pathologic process or with tumor formation. At 0.5 ppm terminal sacrifice the following tissues were examined by light microscopy: lungs, livers, kidneys, lymph nodes, tracheas and grossly visible lesions from all surviving animals; at interim sacrifice grossly visible lesions or tissues where lesions seen at 5 ppm. Recorded parameters included: rats dying or culled during the course of the study, complete necropsy and microscopic exam as described above (except when autolysis precluded evaluation) and the presence and absence of neoplasms. Body weights, terminal organ weights and cumulative mortality, urinalysis, clinical chemistries and hematology did not appear to be altered by chronic HEA exposure. Rats in the 5 ppm treatment group developed yellow staining of the fur and a marginal increase in Mycoplasma-induced pneumonia which was interpreted as being treatment-related. Keratitis was seen in the 0.5 ppm and above dose groups. Chronic inhalation exposure to HEA at a dose of 5 ppm caused minimal toxicological systemic effects. Other than slight (and minimal severity of) keratitis in the eyes in the 0.05 ppm dose group and increased incidence of keratitis and increased severity in the 5 ppm dose group, gross and histopathological examination of tissues showed no indication of significant chronic toxicity or a carcinogenic effect in either the 0.5 or 5 ppm HEA treatment groups (Kociba et al., 1979). It was concluded, that the 0.05 ppm dose group is a Lowest-Observed-Adverse-Effect-Level (LOAEL)(based on slight keratitis; ocular irritation).

As part of the chronic inhalation study described above (Kociba et al., 1979) a detailed pathological examination of the male and female reproductive organs was conducted. In this study, male and females Sprague-Dawley rats were exposed to HEA vapors for 6 hours per day, 5 days/week for 18 months at doses of 0.5 ppm (2.4 mg/m^3) or 5 ppm (24 mg/m^3). The control group consisting of 100 animals of both sexes was exposed to air. After termination of treatment the male and female animals were left for a recovery period of 5 and 6 months respectively before being killed for examination post mortem. The pathological examination indicated that the female rats in the 5 ppm group showed an increased incidence of uterine inflammation as compared to the negative control animals. The incidence of uterine inflammation was 2/21 in controls and 1/3[1] and 11/27 for the 0.5 and 5 ppm groups, respectively. No other statistically significant differences for histopathologic observations of the female

[1] The authors noted that there was a significant amount of pneumonia caused my mycoplasma infection that affected the low dose (0.5 ppm) more than the other dose groups in Kociba et al. (1979).

reproductive organs were found, including the ovaries and the effects in the uterus were not considered by the authors as indicative of reproductive toxicity potential for HEA.

In a study where the developmental toxicity of seven acrylates was investigated (Saillenfait et al., 1999), groups of 25 pregnant rats were exposed to 0, 1, 5 or 10 ppm (0, 4.8, 24 or 48 mg/m^3). HEA was administered by inhalation 6 hrs/day from days 6 through 20 of gestation. Maternal toxicity was demonstrated at 10 ppm as a statistically significant decrease in maternal body weight gain over the entire exposure period, which was also statistically different from controls on days 6-13. A statistically significant decrease in food consumption as compared to controls was also observed for the 10 ppm group on days 6-21. Uteri were removed and weighed, and the number of implantation sites, resorptions, and dead and live fetuses were recorded. Uteri which had no visible implantation sites were stained with ammonium sulfide to detect very early resorptions. Live fetuses were weighed, sexed, and examined for external anomalies including those of the oral cavity. Half of the live fetuses from each litter were preserved in Bouin's solution and examined for internal soft tissue changes. The other half were fixed in ethanol, eviscerated, and then processed for skeletal staining with alizarin red S for subsequent skeletal examination. There were no treatment-related increases in the number of implants, embryo/fetal mortality or fetal malformations observed. There was no treatment effect on fetal body weight. The no-observed-effect-level (NOEL) for maternal toxicity was 5 ppm, the NOEL for developmental effects and fetotoxicity was 10 ppm.

Derivation of Screening Level

The 12-month inhalation exposure in rats (Kociba et al, 1979) was used to set a health protective screening level that protects humans from chronic toxicity. The lowest-observed-adverse-effect-Level (LOAEL), based on corneal inflammation (keratitis), was 0.5 ppm (23.7 mg/m^3). A no-observed-adverse-effect-level (NOAEL) was not identified. The LOAEL was duration-adjusted for continuous exposure as follows:

$LOAEL_{ADJ}$ = LOAEL hours exposed per day x days exposed per week
$LOAEL_{ADJ}$ = 2.4 mg/m^3 x 6/24 x 5/7
$LOAEL_{ADJ}$ = 0.429 mg/m^3

No information was available to determine the human equivalent concentration (HEC) based on ocular irritancy, therefore, the $LOAEL_{ADJ}$ was assumed to be equivalent to the $LOAEL_{HEC}$. A Reference Concentration (RfC) was derived using uncertainty factors (UFs) as follows:

$RfC = (LOAEL_{HEC})/(UF1 \times UF2)$
Where, UF1 = 10 for extrapolation of animal data to humans, and
UF2 = 10 for sensitive individuals
UF3 = 3 for LOAEL to NOAEL extrapolation

A full uncertainty factor of 10 was used for interspecies variability because a dosimetric adjustment factor was unavailable, resulting in additional uncertainty surrounding the animal-to-human extrapolation. The LOAEL to NOAEL extrapolation was reduced from 10 to 3 to account for the slight and minimal ocular keratitis observed at the 0.5 ppm dose level.

The RfC is calculated as follows:

$$RfC = (0.429\ mg/m^3)/(10 \times 10 \times 3) \times 1000 \mu g/mg$$
$$RfC = 1.43\ \mu g/m^3, \text{ rounding to 1 significant figure} \sim 1\ \mu g/m^3$$

Pursuant to Rule 232(1)(a), the ITSL is equal to the RfC. Pursuant to Rule 232(2)(b), the averaging time is annual.

References

Brunn J. et al., (1976) J. Prakt. Chem., 318: 745-755

Kociba, R.J., Keyes, D.J., Schuetz, D.J., Yakel, H.O., Balmer, M.F. and Rampy, L.W. (1979) Results of a Two-Year Inhalation Toxicity Study of 2-Hydroxyethyl acrylate (HEA) in rats. Report of The Dow Chemical Company, Midland, MI.

Leong, B.K.J. and Trice, V.R. (1970) Effects of Repeated Inhalation Exposures of Rats and Single Exposure of Humans to Vapors of Hydroxy Ethyl Acrylate. Report of The Dow Chemical Company, Midland, MI.

Saillenfait, AM, Bonnet, P, Gallissot, F, Protois, JC, Peltier, A and Fabries, JF. (1999) Relative developmental toxicities of acrylates in rats following inhalation exposure. Toxicol. Sci. 48:240-254.

United Nations Environment Programme (UNEP). (2005) Chemical Name: Hydroxyethyl acrylate. Screening Information Data Set (SIDS) Initial Assessment Report For SIAM 20. International Programme on Chemical Safety. World Health Organization.
http://www.inchem.org/documents/sids/sids/818611.pdf