MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Methacrylic Acid (CAS # 79-41-4)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: Methacrylic acid ITSL change in the averaging time from 24 hrs to annual

DATE: December 23, 2015

The current ITSL for methacrylic acid (30 ug/m^3) has a justification (attached) dated September 13, 2007. The averaging time (AT) assigned at that time was 24 hours, as per the default methodology at that time (Rule 232(2)(b)). The current file review concludes that the AT may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is being changed from 24 hours to annual at this time.

INTEROFFICE COMMUNICATION

TO: Methacrylic acid file (CAS # 79-41-4)

FROM: Gary Butterfield

SUBJECT: Screening level for methacrylic acid

DATE: September 13, 2007

Methacrylic acid is also known as MAA, or 2-methyl-2-propenoic acid. Methacrylic acid is a corrosive and reactive liquid with an acrid, repulsive odor. The molecular formula is $C_4H_6O_2$. The molecular weight is 86.1 g/mol. The boiling point of methacrylic acid is 160C. The melting point is 16C. The vapor pressure at 25C is 0.98 mmHg. Major uses for methacrylic acid include chemical intermediate in the formation of esters for polymer manufacture for use in paints, adhesives, and textiles.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH) Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), Michigan Department of Environmental Quality (DEQ) library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (1968 - Sept 2006), National Library of Medicine (NLM) - Toxline, and National Toxicology Program (NTP) Status Report.

This evaluation was conducted to update the review of the scientific literature and develop a final ITSL. The CAS and NLM on-line literature searches for this evaluation were conducted on Sept. 18, 2006. The literature search found that this material is not in EPA's IRIS database.

There are available occupational exposure limits for methacrylic acid by ACGIH TLV and NIOSH REL, both of which are 20 ppm (72 mg/m^3). The OEL was used in the past to derive the interim ITSL of 720 ug/m^3 for methacrylic acid. The documentation for the TLV reported the possibility of methacrylic acid being irritating to skin, eyes, and respiratory tract. This documentation was not too clear on exactly what human exposure to methacrylic acid led to the 20 ppm TLV being set. The potential for irritation from methacrylic acid is considered to be less than the irritation potential for acrylic acid, which also had a TLV of 20 ppm. There apparently has not been any well documented occupational exposures at accurately measured concentrations that could serve as a good basis for these OELs, which places into some question if a screening level based on these OELs makes use of the best available scientific information.

The literature search found a 90-day rat and mouse inhalation study, reported by CIIT (1983) that could be used to calculate an ITSL following the EPA RfC methodology, EPA (1994). A 90-day study meets the minimum qualifications for RfC calculations.

In the 90-day study by CIIT (1983), groups of 20 male and 20 female B6C3F1 mice, Sprague-Dawley rats, and Fischer 344 rats were exposed to 0, 20, 100, or 300 ppm (converts to 0, 72, 360 or 1080 mg/m^3) methacrylic acid for 6 hr/d, 5 d/wk for up to 90 days. In this study, 10 of each sex of each species/strain were sacrificed at the end of the first week – 5 exposures. So, there were only 10 of each sex of each species/strain exposed for the whole 90 days. There was some evidence of anterior portions of the respiratory tract having irritation (inflammation of mucosa, degeneration of epithelium, rhinitis, hyperplasia, etc.). The inflammation was observed in all of the groups, including controls; however, it was more prevalent and severe at higher doses. The highest dose level also had decreased body and liver weights.

The incidence of level A nasal turbinate inflammation was some what variable. Histopathological lesions were graded on a scale of 0 to 5, with 0 representing no effects and 5 representing severe effects. The most sensitive effects, and dose responsive incidences for level A nasal turbinate were observed in male F344 rats and female Sprague-Dawley rats when animals grouped by various severity ratings. In male F344 rats, having a severity rating of 2 or more, the incidence rate was 1/10, 2/10, 2/10, and 9/9 for the control to high dose group respectively. In female Sprague-Dawley rats with a severity rating of 1 or more, the incidence was 2/10, 4/10, 4/10, and 8/10 for the control to high dose group respectively.

Two possible calculations of an ITSL via RfC methodology were conducted – 1) older standard NOAEL/LOAEL method, and 2) the newer BMD method.

In the NOAEL/LOAEL method, the 20 ppm group was considered to be the study LOAEL value. The occurrence of level A nasal turbinate inflammation was only slightly increased in the 20 ppm group.

$LOAEL = 20\ ppm \times 3.52\ mg/m^3/ppm = 72\ mg/m^3$

$LOAEL_{(ADJ)} = 72\ mg/m^3 \times 6/24 \times 5/7 = 13\ mg/m^3$

$LOAEL_{(HEC)} = LOAEL_{(ADJ)} \times RGDR_{et}$

Methacrylic acid is considered to be a Category 1 gas, highly reactive and water soluble causing damage (inflammation) in the upper respiratory tract (extra-thoracic).

$$RGDR_{et} = \frac{(v/SA)_a}{(v/SA)_h} = \frac{(0.264/15)}{(13.8/200)} = \frac{0.0176}{0.069} = 0.255$$

A 400 gram rat has a ventilation rate (v) of 0.264 L/min, and extra-thoracic surface area (SA) of 15 cm^2. The ventilation rate (v) for humans is 13.8 L/min, and an extra-thoracic surface area (SA) of 200 cm^2. EPA (1994).

$LOAEL_{(HEC)}$ = 13 mg/m^3 x 0.255 = 3.3 mg/m^3

$$RfC = \frac{3.3\ mg/m^3}{10 \times 3 \times 3 \times 3} = 11\ ug/m^3$$ 24 hour averaging

The uncertainty factors in the above RfC calculation were a factor of 10 for sensitive humans. A factor of 3 for the subchronic-to-chronic uncertainty was used because the effects on the nasal tissue was observed in the 5-day interim sacrifice animals and did not get significantly increased during the last 12 weeks of exposure. However, as there is no long-term exposure data available, it is not known if these early observed lesions could develop into a more severe lesion maintaining the subchronic-to-chronic factor of three reasonable. The animal to human factor is partially covered by use of the $RGDR_{et}$ in the above $LOAEL_{(HEC)}$ calculation, which allows for a reduction to 3 from the normal 10 used for this factor. The factor of 3 was used for the LOAEL to NOAEL adjustment due to the effects being relatively slight.

In the benchmark dose calculation, the male F344 rats with nasal turbinate level A rhinitis lesions at severity of 2 or greater on the scale of 5 had an incidence rate of 1/10, 2/10, 2/10, and 9/9 for the control to high dose respectively. While the female Sprague-Dawley rat incidence of nasal turbinate level A rhinitis lesions at any severity was 2/10, 4/10, 4/10, and 8/10. The six dichotomous models found there were no significant differences to preclude use of these data sets in developing the BMDL based RfC.

	S-D female	F344 male
model	Level A rhinitis, inflammation	Severity >=2
Gamma	14.01	57.86
Logistic	27.81	29.47
Multi-stage	14.30	23.34
Probit	28.71	27.42
Quantal linear	13.99	-------
Weibull	14.07	47.88
Avg =	18.81	37.19

The six modeled BMDL values for each of the above data sets were all averaged to obtain a BMDL value of 19 ppm (rounded from 18.81) for the female Sprague-Dawley rat combined rhinitis and inflammation, and 37 ppm for the male F344 rats. The BMDL for female rats was selected for deriving the RfC, since it was lower than the male rat BMDL, which indicates female may be more sensitive to nasal inflammation from exposure to methacrylic acid. The following RfC calculations will utilize the same $RGDR_{et}$ as used in the above LOAEL calculations.

BMDL = 19 ppm = 67 mg/m^3

$BMDL_{(ADJ)}$ = 67 x 6/24 x 5/7 = 12 mg/m^3

$BMDL_{(HEC)}$ = 12 x 0.255 = 3.06 mg/m^3

$$RfC = \frac{3.06\ mg/m^3}{10 \times 3 \times 3} = 30.6\ ug/m^3$$ rounded to 30 ug/m^3 with 24 hour averaging

The uncertainty factors in the above RfC calculation were a factor of 10 for sensitive humans. A factor of 3 for the subchronic-to-chronic uncertainty and a factor of 3 for the animal to human factor, which is partially covered by use of the RGDR in the $BMDL_{(HEC)}$ calculation.

An evaluation was also conducted of the 5-day interim sacrifice information on the occurrence of nasal turbinate level A rhinitis using benchmark dose methodology. The interim sacrifice, after 5 days of exposure, indicates this nasal turbinate level A rhinitis lesion appears within only a few days of the start of exposure to methacrylic acid, and doesn't seem to get too noticeably worse or severe with exposure thru 90 days. The mice were found to be less sensitive for these effects than the rats as was also observed in the 90 day results. The female F344 and Sprague-Dawley rats have the best dose responses to exposure with incidence of rhinitis of 0/10, 2/10, 4/10 and 7/10 for female F344 rats, and 0/10, 2/10, 4/10, and 6/9 for the female S-D rats for control to high dose, respectively. The male Sprague-Dawley rats also had this lesion occurring with an incidence of 2/9, 3/10, 4/10, and 6/10. The six dichotomous models found there were no significant differences to preclude use of these data sets in developing the BMDL based RfC. The six modeled BMDL values for each of the above data sets were averaged to obtain a BMDL for each sex and strain of rats. These averaged BMDLs were 23 ppm, 23 ppm, and 28 ppm for the female F344, female Sprague-Dawley, and male Sprague-Dawley rats, respectively. All of these BMDLs are slightly higher than the selected BMDL derived from the 90-day study. Since the 90-day study provides a lower BMDL, and would provide a lower RfC (and ITSL), the 90-day study BMDL will be used to establish the ITSL.

In conclusion, the ITSL is being set at 30 ug/m^3 with 24-hour averaging, based on the 90-day averaged BMDL calculation for the nasal lesions in the female Sprague-Dawley rats. The BMD methodology is the EPA's current preferred methodology for calculation of an RfC.

References

ACGIH. 1991. Documentation of the threshold limit values (6^{th} edition). Note: the latest version of this document came out in 2001, but was not available. The TLV value for methacrylic acid has not changed since the late 1980's.

CIIT. 1983. 90-Day vapor inhalation toxicity study of methacrylic acid in B6C3F1 mice, Sprague-Dawley rats and Fischer 344 rats. CIIT doc # 10915, and EPA OTS doc # FYI-OTS-0685-0415.

EPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066f.

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