MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: Glycidyl methacrylate file (CAS # 106-91-2)

FROM: Gary Butterfield

SUBJECT: Screening level for Glycidyl methacrylate

DATE: July 24, 2006

Glycidyl methacrylate is a colorless liquid at ambient temperatures. It is also known as 2,3-epoxypropyl methacrylate. The molecular formula is $C_7H_{10}O_3$ for this liquid. The molecular weight is 142.1 g/mol. It is highly water soluble. The melting point is less than -10 degrees Celsius. The boiling point is 197 degrees Celsius. The vapor pressure is reported to be 0.36 mmHg at 20C. This material is quite reactive, and known to cause contact irritation upon exposure of skin, eyes and respiratory tract.

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 - Jun 2006), National Library of Medicine (NLM) - Toxline, and National Toxicology Program (NTP) Status Report.

The CAS and NLM on-line literature searches were conducted on June 12, 2006 to evaluate recent published literature. This material is a high production volume chemical. The OECD has taken charge of tabulating available toxicity data in a SIDS. That 2002 SIDS document was identified in this search. This document summarizes many toxicity studies of this chemical. Unfortunately a large number of these studies were either foreign, or published many years ago – not conducted under current testing guidelines, or with old chemicals having unknown purity. Among the more useful studies identified and summarized in the SIDS document, for the purpose of establishing an ITSL, are several unpublished studies conducted by Dow Chemical and submitted to EPA for ToSCA. These studies were available through the EPA OTS library.

In the Landry et al (1996) study, groups of 10 male and 10 female Fischer 344 rats were exposed to glycidyl methacrylate at concentrations of 0, 0.5, 2 or 15 ppm (0, 2.9, 12 or 87 mg/m^3) for 6 hours a day, 5 days a week for 13 weeks. There were no exposure related effects in clinical observations, body weight , urinalysis, clinical chemistry, hematology, or organ weights. At the high dose there was nasal respiratory epithelium hyperplasia in all of the rats resulting in that tissue being 2 to 3 times thicker than in the controls. This pathology was not observed in any animals at the mid-dose level or low dose. This led the authors to conclude that 2 ppm or 12 mg/m^3 was the NOAEL, while the 15 ppm or 87 mg/m^3 is the LOAEL.

In another subchronic study by Mattsson et al (1996), groups of Fischer 344 rats were exposed to 0, 0.5, 2 or 15 ppm (0, 2.9, 12, or 87 mg/m^3) for 6 hours a day, 5 days a week for 13 weeks. Neurotoxic effects were evaluated by functional observation battery (FOB), and motor activity (MA). There also was evoked potential testing of visual (FEP), auditory (ABR), somatosensory (SEP), and caudal nerves (CNAP). There was no evidence of any neurotoxic effects observed at any dose level in this study. Unfortunately there was no nasal tissue histopathology examination reported in the final report. However, there was some mention of clinical observation of enlarged nostrils in the high dose rats, and in a couple of the mid-dose rats. This observation could be evidence of irritation, which can lead to histopathology changes.

The best data for establishment of the screening level is the NOAEL from the Landry et al study which reported detailed histopathology changes in the respiratory tract of exposed rats. The screening level is calculated by using the NOAEL methodology in traditional RfC calculation. The BMD methodology is not appropriate to model in this case, because no data was presented identifying a dose response to the exposures. There was either no response at low doses or all animals responded in the high dose.

In the calculation of the screening level, glycidyl methacrylate is considered to be a category 1 gas due to the observed adverse effects being in the nasal cavity (extra-respiratory). The screening level development generally followed EPA (1994) RfC calculation methodology.

The rat minute volume (Ve) was calculated from EPA (1994) equation 4-4 on page 4-27 using default rat body weight from table 4-5 on page 4-28, and intercept and coefficient values from table 4-6 on page 4-29, as follows.

rat minute vol = $\ln(Ve) = -0.578 + 0.821 \times \ln(0.152) = 2.125$

$Ve = 0.1195$ L/min

The dosimetric adjustment for rat to humans used the regional gas dose ratio (RGDR) for extrathoracic region was determined from EPA (1994) equation 4-18 on page 4-47, using the default surface areas (SA) from table 4-4 on page 4-26. The default human inhalation rate is 20 m^3/d or 13.8 L/min.

$$RGDRet = \frac{[Ve/SAet]a}{[Ve/SAet]h} = \frac{[(0.1195L/min)/(15cm^2)]}{[(13.8L/min)/(200cm^2)]} = \frac{0.007967}{0.069} = 0.1155$$

$NOAEL = 12\ mg/m^3$

$NOAEL_{ADJ} = 12\ mg/m^3 \times 6hr/24d \times 5d/7d = 2.14\ mg/m^3$

$NOAEL_{HEC} = 2.14\ mg/m^3 \times 0.1155 = 0.247\ mg/m^3$

$RfC = (0.247\ mg/m^3)/(10x10x3) = 0.8\ ug/m^3$

Uncertainty factors used in the above calculation included 10 for sensitive individuals and subchronic to chronic extrapolation, and a factor of 3 for animal to human extrapolation.

Typically, a 24 hour averaging time would apply to an ITSL determined by RfC methodology per R232(1)(b). However, R229(2)(b) allows the use of alternative methodologies from R232 to be used in determining an ITSL that is more appropriate based on toxicological grounds and supported by scientific data. Considering the subchronic study duration of Landry et al for the

respiratory tract effects observed, and the ability to also develop a short-term screening level (see below), it is considered appropriate for the ITSL based on the above RfC to have an annual averaging time. The combined short-term (see below) and annual average (above) screening levels will ensure adequate protection against adverse respiratory tract effects from short- and long-term exposure to glycidyl methacrylate.

The short term exposure study reported by Vedula et al (1995) was considered to be the best available data for the establishment of the short term averaging time ITSL. The most sensitive respiratory tract pathology changes in a fairly sensitive species were observed in this study. In the Vedula et al (1995) study, pregnant female New Zealand white rabbits were evaluated for reproductive and developmental effects following exposure to 0, 0.5, 2 or 10 ppm (0, 2.9, 12 or 58 mg/m^3) for 7 hours a day, on gestation days 7 to 19. These exposure levels caused no toxic effects on the developing fetuses. However, maternal respiratory tract histopathology effects were observed at the 2 and 10 ppm exposure levels. This led the authors to find that the NOAEL was 0.5 ppm or 2.9 mg/m^3 for maternal respiratory tract changes.

NOAEL = 0.5 ppm = 2.9 mg/m^3

$NOAEL_{ADJ}$ = 2.9 mg/m^3 x 7hr/24d = 0.85 mg/m^3

The rabbit minute volume (Ve) was calculated from EPA (1994) equation 4-4 on page 4-27 using default rabbit body weight from table 4-5 on page 4-28, and intercept and coefficient values from table 4-6 on page 4-29, as follows.

rabbit minute volume = ln(Ve) = -0.783 + 0.831 x ln(3.1) = 0.157
Ve= 1.17 L/min

The dosimetric adjustment for rabbit to humans used the regional gas dose ratio (RGDR) for extrathoracic region was determined from EPA (1994) equation 4-18 on page 4-47, using the default surface areas (SA) from table 4-4 on page 4-26. The default human inhalation rate is 20 m^3/d or 13.8 L/min.

$$RGDR = \frac{[Ve/SAet]a}{[Ve/SAet]h} = \frac{[(1.17L/min)/(30cm^2)]}{[(13.8L/min)/(200cm^2)]} = \frac{0.039}{0.069} = 0.565$$

$NOAEL_{HEC}$ = 0.85 mg/m^3 x 0.565 = 0.48 mg/m^3

Short term ITSL = (0.48mg/m^3) / (10 x 3) = 16 ug/m^3 24 hour average

Uncertainty factors of 10 for sensitive individuals, and 3 for animal to human extrapolation were used in the above calculation.

For the purpose of complying with R225, both the short term ITSL (16 ug/m3 with 24 hour averaging) and the chronic ITSL (0.8 ug/m3 with annual averaging time) should be met.

References

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

Landry et al. 1996. Glycidyl methacrylate – thirteen-week vapor inhalation toxicity study in Fischer 344 rats. Dow Chemical ToSCA submission -- OTS 0558871

Mattsson et al. 1996. Glycidyl methacrylate – 13-week inhalation neurotoxicity study in Fischer 344 rats. Dow Chemical ToSCA submission -- OTS 0558872.

OECD SIDS. 2002. Glycidyl methacrylate - Screening information data set for high production volume chemicals.

Vedula et al. 1995. Glycidyl methacrylate – inhalation teratology study in New Zealand white rabbits. Dow Chemical ToSCA submission -- OTS 0558853.