MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: Epichlorohydrin File (CAS # 106-89-8)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level for Epichlorohydrin (CAS # 106-89-8)

DATE: April 13, 2015

The initial threshold screening level (ITSL) for epichlorohydrin is 1 ug/m^3 based on an annual averaging time. The ITSL was established on 12/12/1991 based on an EPA Reference Concentration for chronic inhalation exposure (RfC) of $1x10^{-3}$ mg/m^3 (EPA, 1992). The EPA based their RfC determination on a rat and mouse 90-day inhalation study by Quast et al. (NTIS, 1979), which found a NOAEL of 5 ppm for changes in the nasal turbinates.

In the Quast et al. (NTIS, 1979) 90-day study, "groups of B6C3F1 mice, Fischer 344 rats, and Sprague-Dawley rats (10/sex/concentration/strain) were exposed to 0, 5, 25, or 50 ppm (0, 19, 95, or 189 mg/cu.m) epichlorohydrin (99.8% purity), 6 hours/day, 5 days/week (duration adjusted to 3.4, 17, and 34 mg/cu.m, respectively), for 61-62 exposures. Epichlorohydrin vapor was generated by metering the liquid into a warmed vaporization flask then passed through the chamber airflow with compressed air. The dynamic airflow conditions were maintained at 70-75 degrees F and relative humidity at 40-60%. Animals were observed for clinical signs of toxicity and measured biweekly for body weight changes. Clinical chemistry, hematology, and urinalysis were conducted; organ weights were obtained; and gross and histological examination of all tissues, including lungs, nasal turbinates (3-4 sections), liver, kidney, and male reproductive organs was conducted. Animals were sacrificed at 1 month and 3 months (10/concentration) and all parameters were evaluated except that histological observations were made on only five animals per concentration in the control and 50-ppm animals at the interim sacrifice. At the 3-month terminal sacrifice, animals in all groups were evaluated for histopathological effects of the respiratory system, liver, and kidney; other tissues were examined only in the control and 50-ppm groups" (EPA, 1992).

"In rats, epichlorohydrin-related effects in the respiratory epithelium of the nasal turbinates (i.e., inflammation, focal erosions, hyperplasia, and metaplasia), were reported in 25- and 50-ppm F344 rats (males, 9/10, 10/10; females 8/10, 10/10, respectively) and Sprague-Dawley rats (males, 9/10, 10/10; females, 10/10, 10/10, respectively). This effect was observed in all exposed rats in the 50-ppm group examined at the 1-month interim sacrifice

and in none of the controls at 1 or 3 months or in the 5-ppm group at 3 months. Focal effects in the olfactory epithelium and suppurative inflammatory exudate were also observed in male and female rats of both strains after exposure to 50 ppm. Inflammation of the pulmonary region described as mononuclear cell infiltrates or focal pneumonitis was observed in most of the control and exposed rats of both strains, making conclusions about possible effects in the pulmonary region impossible. Inflammation of the nasal turbinates (described as focal subepithelial mononuclear cell infiltrate) was observed in most rats of both strains in the control and 5 ppm groups but not in the 25- and 50-ppm groups. This lesion indicates an underlying inflammatory reaction in these tissues which is not exposure-related. However, the location of this lesion makes it distinct from the epithelial effects observed in the rats exposed to higher concentrations. At the 1- and 3-month sacrifices, the 50-ppm groups in both rat strains (except for the Sprague-Dawley males killed at 3 months) exhibited significant increases ($p<0.05$) in the relative kidney weight compared with controls. Slight increased kidney effects (e.g., dilated tubules, swollen appearance) were also exhibited in female rats exposed to 50 ppm. No other treatment-related effects were observed. The NOAEL of 5 ppm epichlorohydrin was determined for nasal turbinate injury [rat NOAEL(HEC) values range from 0.36 for female F344 rats to 0.70 for male Sprague-Dawley (SD) rats, due to differences in ventilation volume; RGDR = 0.107 – 0.206 based on respiratory effects in the extrathoracic region]. A NOAEL for kidney effects is identified at 25 ppm [NOAEL(HEC) = 17 mg/cu.m]. The respiratory effects in rats are used for derivation of the RfC because of the greater severity of the lesion in rats, the involvement of respiratory and olfactory epithelium, and the lower calculated NOAEL(HEC)" (EPA, 1992).

"Results in mice after 3 months showed focal erosion, hyperplasia, and metaplasia in the respiratory epithelium of the nasal turbinates in 0/10, 0/9, 8/8, and 10/10 males and in 0/9, 0/9, 10/10, and 9/9 females of the 0, 5-, 25-, and 50-ppm groups, respectively. This finding was also reported in 4/5 males and 5/5 females in the 50-ppm group compared with 0/10 in the controls at the 30-day sacrifice. Suppurative inflammatory exudate or mucus in the lumen of the nasal turbinates were reported in 7 males and 7 females in the high-concentration group. Focal effects in the olfactory epithlium were reported in only one female in the 50-ppm group. There were no other clearly exposure-related effects observed. However, 2, 1, 0, and 0 males and 9, 9, 0, and 0 females in the control, 5-, 25-, and 50-ppm groups, respectively, exhibited focal subepithelial mononuclear cell infiltrate in the nasal turbinates. This lesion indicates an underlying inflammatory reaction in these tissues that is not exposure-related. However, the location of this lesion makes it distinct from the epithelial effects in the groups exposed to higher concentrations. Inflammatory reactions in the tracheobronchiolar and pulmonary region, which may have been treatment related, were observed in a few animals in the high-concentration groups. All other microscopic findings were interpreted to be spontaneous. There was no indication that the investigators test for viral infection. A NOAEL of 5 ppm was established for changes in the nasal turbinates of mice (HEC = 0.41 mg/cu.m, based on respiratory tract effects in the extrathoracic region in females). The HEC for nasal effects is essentially identical in rats and mice. The lesser severity of the lesion in mice may be due to their ability to reduce their ventilation in

response to an irritant to a greater extent than rats (see discussion of Kane et al., 1979). Mice have previously shown an ability to decrease their minute volume by up to 75% as compared with a maximal 45% reduction in rats when exposed to formaldehyde (Barrow et al., 1983; Chang et al., 1983). This study supports the finding of nasal effects at 25 and 50 ppm in rats" (EPA, 1992).

The EPA used a total uncertainty factor of 300 (10 for sensitive human subpopulations; 3 for interspecies extrapolation; and 10 for subchronic to chronic uncertainty factor). The EPA also used the following conversion factors: MW = 92.53. Assuming 25 degrees C and 760 mmHg:

$$NOAEL\ \left({}^{mg}/_{m^3}\right) = \frac{5\ ppm\ \times 92.53}{24.45} = 19\ {}^{mg}/_{m^3}$$

$$NOAEL_{ADJ} = NOAEL\ \left({}^{mg}/_{m^3}\right) \times \frac{6\ hours}{24\ hours}\ \times \frac{5\ days}{7\ days} = 3.4\ {}^{mg}/_{m^3}$$

The NOAEL (HEC) was calculated for a gas:respiratory effect in the extrathoracic region. MVa (subchronic, female F344 rat) = 0.14 cu.m/day, MVh = 20 cu.m/day, Sa(ET) = 11.6 sq.cm, Sh(ET) = 177 sq.cm.

$$RGDR = \frac{(\frac{MVa}{Sa})}{(\frac{MVh}{Sh})} = \frac{(\frac{0.14\ {}^{m^3}/_{day}}{11.6\ cm^2})}{(\frac{20\ {}^{m^3}/_{day}}{177 cm^2})} = 0.107$$

$$NOAEL_{HEC} = 3.4\ {}^{mg}/_{m^3}\ \times RGDR = 0.36\ {}^{mg}/_{m^3}$$

$$RfC\ {}^{mg}/_{m^3} = \frac{0.36\ {}^{mg}/_{m^3}}{300} = 0.001\ {}^{mg}/_{m^3} = 1\ {}^{\mu g}/_{m^3}$$

Therefore the ITSL is 1 µg/m^3. According to Rule 232(2)(b) a 24-hour averaging time period should be used, but as this ITSL is based on a 90-day study it is appropriate to utilize a longer averaging time, which would be an annual averaging time. The ITSL for epichlorohydrin is 1 µg/m^3 based on an annual averaging time.

References:

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