MICHIGAN DEPARTMENT OF NATURAL RESOURCES & ENVIRONMENT

INTEROFFICE COMMUNICATION

TO: File for Methylene diphenyl diisocyanate (CAS# 101-68-8) and polymeric methylene diphenyl diisocyanate file (CAS# 9016-87-9)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 23, 2017

SUBJECT: Methylene diphenyl diisocyanate (CAS# 101-68-8) and polymeric methylene diphenyl diisocyanate (CAS# 9016-87-9) change in the averaging time from 24 hours to annual

The initial threshold screening level (ITSL) for methylene diphenyl diisocyanate is 0.6 µg/m^3 based on an annual averaging time. The ITSL was originally established on 5/23/2014 and was set at 0.6 µg/m^3 based on a 24-hour averaging time. The ITSL was based on a well conducted 24-month inhalation study Reuzel et al, (1990) using (SPF)-bred Wistar rats of the Cpb:WU strain (60/sex/dose) exposed to 0, 0.2, 1.0, or 6.0 mg/m^3 via whole body aerosols of polymeric methylene diphenyl diisocyanate (PMDI) for 6 hours/day, 5 days/week, for 24-months. The most sensitive effect of hyperplasia of the olfactory epithelium was used by the EPA in their derivation of an RfC of 6E-4 mg/m^3. As the key study used to derive the ITSL is a 24-month inhalation study, the averaging time is appropriately set at annual. Therefore, the averaging time is being changed from 24 hours to annual at this time.

References:

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality

EPA. 1998. Integrated Risk Information System. Methylene diphenyl diisocyanate (monomeric MDI) and polymeric MDI (PMDI) (CASRN 101-68-8, 9016-87-9). Available online at: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=529

Reuzel PGJ, Arts JHE, Lomax LG, Kuijpers MJM, Kuper CF, Gembardt C, Feron VJ, and Loser E. 1994. Chronic inhalation toxicity and carcinogenicity study of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. Fundam. Appl. Toxicol. 22: 195-210.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: Methylene diphenyl diisocyanate file (CAS # 101-68-8) and polymeric methylene diphenyl diisocyanate file (CAS # 9016-87-9)

FROM: Doreen Lehner

DATE: May 23, 2014

SUBJECT: Screening level for methylene diphenyl diisocyanate (CAS # 101-68-8) and polymeric methylene diphenyl diisocyanate (CAS # 9016-87-9)

The Initial Threshold Screening Level (ITSL) for methylene diphenyl diisocyanate (CAS # 101-68-8) and for polymeric methylene diphenyl diisocyanate (CAS # 9016-87-9) is 0.6 µg/m^3 based on a 24-hour averaging time. These ITSLs are based on the EPA RfC (EPA 1998).

Methylene diphenyl diisocyanate also known as monomeric MDI, 1,1'-methylenebis (4-isocyanatobenzene), and 4,4'-methylenebis (phenyl isocyanate) appears as white to light yellow, odorless flakes and is a liquid above 99°F. The molecular weight is 250.26 g/mol and the molecular formula is $CH_2(C_6H_4NCO)_2$.

Polymeric methylene diphenyl diisocyanate also known as polymeric MDI or PMDI, MDI oligomer, and polymeric isocyanate is a liquid with a molecular weight of approximately 400 g/mol.

A CAS search was conducted by MDEQ on March 3rd of 1995. Subsequent to that, EPA (1998) established an inhalation reference concentration (RfC) for methylene diphenyl diisocyanate of 6E-4 mg/cu.m based on a study by Reuzel et al, (1990, 1994b) on chronic inhalation of aerosol in rats showing hyperplasia of the olfactory epithelium as the critical effect.

In the Reuzel et al., (1990) study, "specific-pathogen-free (SPF)-bred Wistar rats of the Cpb: WU strain (60/sex/exposure level) were exposed whole-body to aerosols of polymeric methylene diphenyl diisocyanate (PMDI). The test material was a dark brown liquid with an average molecular weight of about 400 and each batch received from the manufacturer contained 47% monomeric MDI. The remaining 53% was described as "polymeric" MDI. [Note: PMDI refers to a mixture containing about 50% monomeric MDI and 50% trimeric species and higher molecular weight oligomers (Ulrich, 1983); this composition, which is very similar to that used in the workplace, renders the material semisolid and suitable for aerosol generation.] The test material was kept at room temperature under 'common laboratory conditions.' This is interpreted to mean that the test material was stored under an inert gas. If unprotected, MDI reacts with water to form carbon dioxide" (EPA, 1998).

"The rats were exposed for 6 h/day, 5 days/week, for 24 mo. to nominal exposure levels of 0, 0.2, 1.0, and 6.0 mg/cu.m. A satellite group of rats (10/sex/exposure level) was exposed similarly for 12 mo. and examined histopathologically at the end of exposure. The mean actual values as measured by gravimetry were within plus or minus 10% of nominal values. Thus, nominal values will be used in the following discussion. The duration-adjusted exposure levels are 0, 0.036, 0.18, and 1.1 mg/cu.m. Particle size determinations were made weekly with a cascade impactor. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (in parentheses) corresponding to the exposure levels were 0, 0.68 µm (2.93), 0.70 µm (2.46), and 0.74 µm (2.31), respectively. Gross observations and organ weights were obtained on all animals. Histopathological observations were

made on the lungs, mediastinal lymph nodes, and nasal cavity (six levels) on all animals and in forty-three other tissues in controls and animals exposed to 6 mg/cu.m" (EPA, 1998).

"Histologic evidence of damage at the 24-month necropsy of the main group involved the same tissues as at 12 months, although the severity had increased in nasal and pulmonary tissues. Basal cell hyperplasia was evident in the olfactory epithelium of the nasal tract of males (14/60, 13/60, 26/60, and 32/60 at the 0, 0.2, 1.0, and 6.0 mg/cu.m, respectively) and females (4/60, 8/60, 8/60, and 49/59 at 0, 0.2, 1.0, and 6.0 mg/cu.m, respectively). Statistical significance was reached in males at the mid and high concentrations and only at the high concentration in females. It was often accompanied by Bowman's gland hyperplasia, which was significant in males at 1 and 6 mg/cu.m. Olfactory epithelial degeneration was elevated significantly in males and females only at 6 mg/cu.m. In the lung, there was increased severity in the accumulation of pigment-laden macrophage in alveolar duct lumina (incidence in males: 0/60, 3/60, 21/60, and 60/60; females: 0/59, 1/60, 23/60, and 59/59) and in localized fibrotic changes (males: 1/60, 0/60, 9/60, and 44/60; females: 0/59, 0/60, 4/60, and 48/60). Localized alveolar duct epithelialization was increased significantly in both males and females exposed to 1 and 6 mg/cu.m. Localized alveolar bronchiolization was significant in both sexes exposed to 6 mg/cu.m. Accumulation of yellow pigment in the mediastinal lymph nodes was noted in males (incidence: 0/59, 0/53, 9/51, and 50/58) and females (incidence: 0/53, 1/57, 3/50, and 43/55). The accumulation of macrophage and the localization of tissue damage in the area of macrophage accumulation suggest that the lung effect is due primarily to toxicity of the macrophage (with secondary damage), although some of the effects were described as being distributed evenly throughout the lungs. There were no histological effects in any of the other organ systems examined" (EPA, 1998).

"The information obtained in this chronic study suggests that the NOAEL is 0.2 mg/cu.m (duration-adjusted concentration = 0.036 mg/cu.m) and a LOAEL of 1.0 mg/cu.m (duration-adjusted concentration = 0.18 mg/cu.m) for respiratory tract effects in both pulmonary and extrathoracic regions. The RfC was derived using benchmark concentration (BMC) analysis on basal cell hyperplasia of the olfactory epithelium (males only). The BMC approach was used because it takes into consideration the shape of the concentration-response curve, whereas the NOAEL selection is based solely on study concentrations employed. Given the apparent sensitivity of the male to basal cell hyperplasia and the expression of an elevated incidence of both basal cell hyperplasia and olfactory degeneration at both the mid and high concentrations, it is not possible to differentiate basal cell hyperplasia, on the basis of either the interim or final sacrifice histopathological results, as a compensatory response to olfactory degeneration. Thus, it is prudent to regard basal cell hyperplasia as an adverse response. This critical effect was chosen over localized pulmonary fibrosis because; after HECs are compared, the nasal effects would yield a more conservative RfC. Because the test mixture in the Reuzel et al. study (1990, 1994b) was of a composition that is typically used during polyurethane foam manufacturing, the results of this study are more relevant to potential exposure of individuals in ambient environments than are those associated with the pure MDI used by Hoymann et al. (1995)…. For this reason, the results of the Reuzel study were used in RfC derivation" (EPA, 1998).

Monomeric MDI has a molecular weight of 250.26 g/mol. BMC10 (ADJ) was obtained by running the BMC software program using concentrations from the Reuzel et al. (1994b) study adjusted for 24 hours/day and 7 days per week. "The THRESH polynomial regression model, developed by Clement International specifically for quantal endpoints was used in the BMC analysis. The model was used to calculate extra risk, defined as the fraction of animals that would respond to a dose among animals who otherwise would not respond. The model was run at two specified levels of risk, 5% and 10%, using the concentrations and responses for nasal olfactory basal cell hyperplasia in male rats from the Reuzel et al. (1994b) study. The BMC10 [HEC] was calculated for a particle: respiratory effect in the extrathoracic (ET) region. Maximum likelihood estimates (MLE) and BMC values (i.e. lower 95% confidence bound on MLE) were derived for each risk level. With both models at the 5%

and 10% risk levels, the MLEs were 0.10 and 0.22 mg/cu.m, respectively. Results from both models indicated that the BMCs provided acceptable fits to the data. The goodness-of-fit p value was 0.09. The BMCs were 0.07 and 0.14 mg/cu.m, respectively. The BMC10 values for nasal olfactory degeneration and for basal cell hyperplasia were nearly identical (0.14 mg/cu.m versus 0.18 mg/cu.m, respectively)" (EPA, 1998).

"The regional deposited dose ratio (RDDR) was calculated for each region of the respiratory system according to a computer program based on the rationale and empirical data described in EPA (1994). The RDDRs for the particles having a MMAD = 0.68 μm and sigma g=2.93 [based on particle deposition modeling as described in EPA (1994), Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity, was calculated using current RDDR software as] 0.453 for the extrathoracic and 0.910 for the thoracic regions. [The default body weight (462 gm) for the male Wistar rat was taken from Table 4.5 (EAP, 1994), Methods for Derivation of Inhalation Reference Concentrations and Applications of Inhalation Dosimetry, and used as input to the RDDR program. BMC10 (HEC) = BMC10 (ADJ) RDDR (ET) = 0.06 mg/cu.m.] The resulting BMC10 (HEC) associated with nasal effects is 0.06 mg/cu.m" (EPA, 1998).

References

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

EPA. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, EPA/600/8-90/066F, dated October 1994.

EPA. 1998. Integrated Risk Information System. Methylene diphenyl diisocyanate (monomeric MDI) and polymeric MDI (PMDI) (CASRN 101-68-8, 9016-87-9). Retrieved data on 5/19/2014. Available online at: http://www.epa.gov/iris/subst/0529.htm

Hoymann HG, Buschmann J, and Heinrich U. 1995. Examinations about the chronic toxicity/carcinogenicity of 4,4'-methylene diphenyl diisocyanate (MDI). Fraunhofer-Institut fur Toxikologie and Aerosolforschung, Hannover, Germany. Report No. 116-06-084 (in German).

Reuzel PGJ, Arts JHE, Kuypers MHM, and Kuper CF. 1990. Chronic toxicity/carcinogenicity inhalation study of polymeric methylene diphenyl diisocyanate aerosol in rats. Prepared by the Civo Institute for the International Isocyanate Institute. Report No. V 88.122, 1990.

Reuzel PGJ, Arts JHE., Lomax LG, Kuijpers MHM, Kuper CF, Gembardt C, Feron VJ, and Loser E. 1994. Chronic inhalation toxicity and carcinogenicity study of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. Fundam. Appl. Toxicol. 22:195-210.

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