American Chemistry Council | Aliphatic Diisocyanates Panel

Submitted Via Electronic Mail

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Re: California OEHHA Proposed RELs for Hexamethylene Diisocyanate Monomers and Polyisocyanates

Dear Dr. Budroe,

The American Chemistry Council's Aliphatic Diisocyanates Panel[1] ("Panel") submit the attached comments to the California Office of Health Hazard Assessment ("OEHHA") regarding the proposed reference exposure levels ("RELs") for Hexamethylene Diisocyanate Monomers and Polyisocyanates ("HDI"). The Panel believes that the proposal to develop the HDI RELs is unnecessary and lacks adequate scientific basis. As such, we urge OEHHA to withdraw its proposal.

Thank you for considering our attached comments. If you have any questions or require additional information, please contact me at sahar_osman-sypher@americanchemistry.com or 202 249 6721.

Sincerely,

Sahar Osman-Sypher
Director, Aliphatic Diisocyanates Panel

Attachment: Panel Comments on CA OEHHA Proposed RELs for HDI Monomers and Polyisocyanates

[1] The Aliphatic Diisocyanates Panel represents the U.S. companies that manufacture or import hexamethylene diisocyanate (HDI), isophorone diisocyanate (IPDI) and methylene dicyclohexyl diisocyanate (HMDI). The Panel members include Covestro, Evonik, and Vencorex.

AMERICAN CHEMISTRY COUNCIL
ALIPHATIC DIISOCYANATES PANEL
COMMENTS ON
CALIFORNIA OFFICE OF ENVIRONMENTAL HEALTH
HAZARD ASSESSMENT
PROPOSED REFERENCE EXPOSURE LEVELS FOR
HEXAMETHYLENE DIISOCYANATE
(MONOMERS AND POLYISOCYANATES)

EXPOSURE

The OEHHA Technical Support Document (TSD) for the Derivation of Noncancer Reference Exposure Levels (RELs) states that the objective of the document is to derive acute, 8-hr, and chronic inhalation RELs for use in risk assessments to evaluate the potential for adverse noncancer public health impacts from facility emissions or similar localized sources in the Air Toxics Hot Spots Program.

HDI and HDI based polyisocyanates are manufactured in closed systems. During normal operating conditions, they would not be expected to be released to the air, soil or water. Procedural and/or control technologies are used to minimize emissions and potential exposure during cleaning and maintenance activities. HDI is converted in closed systems to HDI-based products (polyisocyanates), which at most would be expected to contain up to 1% free (residual unreacted) HDI monomer.

HDI based products are used primarily by industrial customers as binders or hardeners to manufacture coatings, adhesives, sealants or elastomers. Releases of HDI into the environment would be expected to be very low as a result of the physical/chemical characteristics associated with HDI monomer and HDI-based polyisocyanates. Diisocyanates are highly reactive in the environment, forming insoluble polyureas that are chemically and biologically inert. Therefore, the derivation of RELs for these substances to evaluate the potential health impacts from facility emissions is unnecessary.

The EPA School Air Monitoring Project monitored the air in 22 states and around 62 schools. The schools were located near industrial facilities or in urban areas. Computer models were used to determine the air toxics that might be present at elevated levels in the outdoor air near the school. Air samples were collected and analyzed. Monitoring failed to detect any diisocyanates, including HDI, in any sample. This data supports the conclusion that diisocyanates should not be an air pollutant of concern for the general population, even near industrial facilities. More information can be found on the EPA website: https://www3.epa.gov/air/sat/index.html.

ACUTE HDI MONOMER REL

OEHHA used the study from Shiotsuka et al. 2006 to set the acute REL for HDI monomer. The Shiotsuka study was a 3 week, 5 hours per day, 5 days per week exposure study. The authors of the study determined that the No Observed Adverse Effect Level (NOAEL) was 0.0175 ppm. The authors described the effects observed at 0.005 ppm as subtle adaptive epithelial responses to injury and not as an adverse effect. Two additional studies with exposure durations of 19 and 49 days did not display any histopathological effects at 0.005 ppm (Astroff et al., 2000a; Astroff et al., 2000b). We believe that OEHHA should use the NOAEL as stated in the Shiotsuka et al. 2006 study for setting this REL. This REL is for acute exposures and using a subchronic exposure study as the basis is already unnecessarily conservative. Setting a lower NOAEL based on an adaptive response observed in a subchronic exposure study is ultra-conservative and not scientifically warranted. Therefore, the acute REL should be recalculated using the NOAEL of 0.0175 ppm. The HDI Monomer Acute REL should be 4 ppb, not 0.1 ppb.

Time adjust 0.0175 x 5 = 0.0875 ppm
HEC 0.0875
REL 0.0875 / 200 = 4 ppb

ACUTE HDI POLYISOCYANATE REL

OEHHA used a default n = 3 value to calculate the time extrapolation for this REL. OEHHA states that this is because of different chemical, physical, and toxicological properties of HDI polyisocyanate aerosols compared to HDI monomer. However, in the acute HDI monomer time extrapolation, one of the Pauluhn studies cited by OEHHA in support of the use of n=1 is a study conducted on HDI polyisocyanates (Pauluhn, 2002). Therefore, we believe that n=1 in the time extrapolation is also appropriate for the Acute HDI polyisocyanate REL. Recalculation with the corrected time extrapolation would result in a HDI-Based Polyisocyanate Acute REL of 14 ug/m^3, not 4.5 ug/m^3.

Time adjust 1.1 x 6 = 6.6 mg/m3
HEC 6.6 x 0.45 = 2.97 mg/m3
REL 2.97/200 = 14.8 ug/m3

8 HR AND CHRONIC HDI MONOMER REL

The 8hr and Chronic RELs for HDI monomer are based on the Cassidy et al. study from 2010. OEHHA is using a NOAEL of 0.78 ppb for this study. The Cassidy study detailed air monitoring data which ranged from non-detectable to 31 ppb. The mean value of the collected air samples was 0.78 ppb – this number does not represent the NOAEL. None of the HDI exposed workers in the study – including those exposed to 31 ppb - displayed significantly accelerated annual decline in force expiratory volume after 1 second (FEV-1), compared to matched controls. In addition, no cases of adult onset asthma, beyond those present at the time of hire and no cases of occupational asthma from any cause, including HDI were identified. The authors stated that the study supports the TLV-TWA of 5 ppb. The presence of exposures above 5 ppb in this study and the lack of identified lung decrement suggests that 0.78 ppb should not be used

as the NOAEL for this study. Since 5 ppb has been observed to be protective for workers and these RELs are set for the general population, 5 ppb should be the minimum starting point and the UF should be applied to this number, not 0.78 ppb. Recalculation with this NOAEL results in a HDI Monomer 8-Hour REL of 0.036 ppb, not 0.006 ppb and a HDI Monomer Chronic REL of 0.182 ppb, not 0.003 ppb.

8 hr

Time adjust 5 x 5/7 = 3.57 ppb
REL 3.57 / 100 = 0.036 ppb

Chronic

Time adjust 5 x 10/20 x 5/7 = 1.785
REL 1.785 / 100 = 0.018 ppb

8 HR HDI POLYISOCYANATE REL

There are several errors in the calculation of the 8hr REL for HDI polyisocyanates. The time adjusted exposure was calculated incorrectly. The hours per day correction used by OEHHA was 6/24, when the correction should have been 6/8. The time adjusted exposure should be 3.214 mg/m^3, not 1.0714 mg/m^3.

3 mg/m3 x 6/8 x 5/7 x 20/10 = 3.214

In addition, a subchronic UF was added to this REL. According to the TSD document, this factor only applies to Chronic RELs (page 48). This UF should be 1 and not 2. Therefore, the total UFs for this REL should be 600 and not 1200.

Total UC: 2 x 3 x 10 x10 = 600

With these 2 corrections made, the final REL should be 4.5 ug/m^3 and not 0.8 ug/m^3.

HEC 3.214 x 0.84 = 2.7
REL 2.7/600 = 4.5 ug/m3

UNCERTAINTY FACTORS THAT APPLY TO MULTIPLE RELS

OEHHA has inappropriately applied overly conservative UFs to derive the RELs. The use of these ultra conservative default UFs is inconsistent with realistic conditions of use, is scientifically unwarranted, and will lead to inappropriate outcomes.

The **interspecies toxicodynamic** UF of 3 used for multiple RELs to account for metabolic variability is inappropriate. The UF is not required because the observed effect on the respiratory tract is the result of a direct acting irritant and not an indirect effect dependent on metabolism. This conclusion is based on reports that direct acting irritants administered to rodents typically induced lesions in the olfactory epithelium and in the respiratory epithelium (Jiang et al., 1983; Gaskell, 1990; Abdo et al., 1998).

Available evidence demonstrates that both HDI monomer and HDI polyisocyanates are direct, local acting toxicants with no systemic effects. Therefore, the 3 fold interspecies toxicodynamic UF for metabolic variability is unwarranted; a UF of 1 would be more appropriate.

The 8-hr and chronic RELs use an **intraspecies toxicokinetic** UF of 10 based on the rationale that genotypic variations are involved in the development of isocyanate induced asthma in workers. OEHHA believes there is also a wide variation in response to isocyanate exposure among the general population. We believe that genotypic variations in metabolic enzymes are not relevant. HDI monomer and HDI polyisocyanates are very reactive substances that interact mainly at the site of contact, either the nasal cavity (HDI vapor) or respiratory tract (HDI polyisocyanate). In vitro and in vivo study data indicates that glutathione (GHS) is the primary reaction target for HDI and HDI homopolymers. (Pauluhn 2000; Wisnewski et al. 2005; Wisnewski et al. 2013). The role for genotypic variation in glutathione transferases (GSTs) is negated by the fact that GSTs are not required for the reaction of isocyanates with glutathione. Also, the effects observed are likely due to the ability of isocyanates to bind to cell membrane proteins in the pulmonary epithelium. Toxicokinetics and genotypic variations in metabolic enzymes, have not been shown to play a role in these direct effects on the olfactory epithelium. Thus, a toxicokinetic UF of greater than 1 is not justified. In addition, page 65 of the TSD document states that OEHHA will apply a UF of 10 as a default for gases acting systematically and for particles that involve systemic exposure. Neither HDI monomer nor HDI polyisocyanate act systemically. The evidence shows they both act through local irritant effects, rendering the UF of 10 unwarranted.

OEHHA's own TSD document (page 66) states that a UF to account for toxicodynamic differences between individuals has generally been assigned a default value of 3. However, for the 8-hr and chronic RELs, OEHHA uses an **intraspecies toxicodynamic** UF of 10 to account generically for hypothetical differences in the way HDI may affect different age groups and specifically for the purported greater sensitivity of infants and children to HDI-induced decrements in lung function. An intraspecies toxicodynamic UF of 10 is not supported by scientific evidence, which indicates children are actually less sensitive to diisocyanate induced lung decrements. Children appear less sensitive to lung decrements associated with diisocyanate induced asthma because diisocyanate induced asthma is primarily a T-helper 1 (Th1) driven process, while childhood asthma is a T-helper 2 (Th2) driven process. First, the exposure likelihood is minimal as evidence by the EPA School Air Monitoring Project mentioned earlier. In addition, there is evidence that children are at a lower risk of diisocyanate induced asthma than adults. Speculative childhood exposure to HDI combined with the observation that humans exhibit a dominant humoral (Th2) responsiveness at birth supports the claim that young children are not at a greater risk for the development of HDI-induced asthma. Research from other isocyanates (toluene diisocyanate, TDI) has demonstrated that isocyanate asthma is not Th2 driven. It is clear that the pathophysiology of childhood asthma and diisocyanate induced occupational asthma are different. While childhood asthma is characterized by the actions of Th2 type interleukins as well as the presence of IgE antibodies and eosinophilia (Levine and Wenzel, 2010; Liu and Wisnewski, 2003), workers diagnosed with diisocyanate asthma lack an

association with atopy and exhibit a very low prevelance of IgE antibodies as well as a very high prevelance of CD8+ T (Th1) cells (Bernstein et al., 2002; Cartier et al;., 1989,; Del Prete et al., 1993; Finotto et al., 1991; Maestrelli et al., 1994; Ott et al., 2007; Tee et al., 1998). These characteristics indicate that diisocyanate asthma is primarily a Th1 driven pathway. We believe a lower UF is warranted and the maximum UF should be 3.

CONCLUSION

In conclusion, the Panel believes that the CA OEHHA's proposal to develop RELs for HDI monomers and polyisocyanates is unnecessary, lacks scientific basis, and should be withdrawn. Since potential exposures to HDI are primarily limited to occupational settings and not the general public, development of RELs for HDI to protect the general public is an unnecessary use of OEHHA resources without commensurate public health benefit. If OEHHA decides to continue to derive RELs for these substances, we urge OEHHA to consider the Panel comments.

REFERENCES

Abdo KM, Haseman JK, Nyska A. (1998) Isobutyraldehyde administered by inhalation (whole body exposure) for up to thirteen weeks or two years was a respiratory tract toxicant but was not carcinogenic in F344/N rats and B6C3F1 mice. Toxicol Sci 42: 136-51.

Astroff AB, Sheets LP, Sturdivant DW, Stuart BP, Shiotsuka RN, Simon GS, Andrews LS. (2000a) A combined reproduction, neonatal development, and neurotoxicity study with 1,6-hexamethylene diisocyanate (HDI) in the rat. Reprod Toxicol 14(2): 135-46.

Astroff AB, Sturdivant DW, Lake SG, Shiotsuka RN, Simon GS, Andrews LS (2000b)_Development toxicity of 1,6-hexamethylene diisocyanate (HDI) in the Sprague-Dawley rat. Teratology 62(4): 205-13.

Bernstein DI, Cartier A, Cote J, Malo JL, Boulet LP, Wanner M, Milot J, L'Archeveque J, Trudeau C, Lummus Z. (2002) Diisocyanate antigen-stimulated monocyte chemoattractant protein-1 synthesis has greater test efficiency than specific antibodies for identification of diisocyanate asthma. Am J Resir Crit Care Med. 166: 445-450.

Cartier A, Grammer L, Malo JL, Lagier F, Ghezzo H, Harris K, Patterson R.(1989) Specific serum antobidies against isocyanates: association with occupational asthma. J Allergy Clin Immunol 84: 507-514.

Cassidy LD, Molenaar DM, Hathaway JA, Feeley TM, Cummings BJ, Simpson P and Li SH (2010). Trends in pulmonary function and prevalence of asthma in hexamethylene diisocyanate workers during a 19-year period. J Occup Environ Med 52(10): 988-94.

Del Prete GF, De Carli M, D'Elios MM, Maestrellio P, Ricci M, Fabbri L, Romagnani S. (1993) Allergen exposure induces the activation of allergen-specific Th2 cell sin the airway mucosa of patients with allergic respiratory disorders. Eur J Immunol. 23: 1445-49.

Finotto S, Fabbri LM, Rado V, Mapp CE, Maestrelli P. (1991) Increase in numbers of CD8 positive lymphocytes and eosinophils in peripheral blood if subjects with late asthmatic reactions induced by toluene diisocyanate. Br J Ind Med 48: 116-121.

Gaskell BA. (1990) Nonneoplastic changes in the olfactory epithelium – experimental studies. Environ Health Perspect. 85: 275-89.

Jiang XZ, Buckley LA, Morgan KT. (1983) Pathology of toxic responses to the RD50 concentration of chlorine gas in the nasal passages of rats and mice. Toxicol Appl Pharmacol. 71: 225-36.

Maestrelli P, Del Prete GF, De Carli M, D'Elios MM, Saetta M, Di Stefano A, Mapp CE, Romagnani S, Fabbri LM. (1994). CD8T-cell clones producing interleukin-5 and interferon-gamma in bronchial mucosa of patients with asthma induced by toluene diisocyanate. Scand J Work Environ Health 20: 376-381.

Ott MG, Jolly AT, Burhert AL, Brown WE. (2007) Issues in diisocyanate antibody testing. Crit Rev Toxicol 37: 567-585.

Tee RD, Cullinan P, Welch J, Sherwood Burge P, Newman-Taylor AJ. (1998) Specific IgE to isocyanates: a useful diagnostic role in occupational asthma. J Allergy Clin Immunol 101: 709-715.

Pauluhn J. (2000) Inhalation toxicity of 1,6-hexamethylene diisocyanate homopolymer (HDI-IC) aerosol: results of single inhalation exposure studies. Toxicol Sci. 58(1): 173-81.

Pauluhn J (2002) Short-term inhalation toxicity of polyisocyanate aerosols in rats: comparative assessment of irritant-threshold concentrations by bronchoalveolar lavage. Inhal Toxicol 14(3): 287-301.

Redlich CA, Karol MH. (2002) Diisocyanate asthma: clinical aspects and immunopathogenesis. Int Immunopharmacol. 2: 213-24.

Shiotsuka RN, Stuart BP, Sangha GK, Sturdivant DW and Hoss H (2006). Subacute inhalation exposure of rats to 1,6-hexamethylene diisocyanate with recovery period. Inhal Toxicol 18(9): 659-65.

Wisnewski AV, Liu Q, Liu J, Redlich CA. (2005) Glutathione protects human airway proteins and epithelial cells from isocyanates. Clin Exp Allergy 35(3): 352-7.

Wisnewski AV, Mhike M, Hettick JM, Liu J, Siegel PD (2013) Hexamethylene diisocyanate (HDI) vapor reactivity with glutathione and subsequent transfer to human albumin, Toxicology In Vitro 27(2): 662-71.