American Chemistry Council | Aliphatic Diisocyanates Panel

February 21, 2019

Jim Behrmann, Panel Liaison
Scientific Review Panel on Toxic Air Contaminants
Air Resources Board
P.O. Box 2815
1001 I Street
Sacramento, California 95812
jim.behrmann@arb.ca.gov

Re: OEHHA Proposed RELs for Hexamethylene Diisocyanate (Monomer and Polyisocyanates)

Dear Mr. Behrmann,

The American Chemistry Council's Aliphatic Diisocyanates Panel (Panel) [1] respectfully submits the attached comments to the members of the California Scientific Review Panel on Toxic Air Contaminants (SRP) in regards to the proposed reference exposure levels (RELs) for Hexamethylene Diisocyanate (Monomer and Polyisocyanates) (HDI). We believe that the Office of Environmental Health Hazard Assessment (OEHHA) has not adequately addressed several issues raised by the Panel when the Agency published its response to public comments[2] and subsequent SRP review draft documents for the HDI RELs[3] on February 4, 2019. As such, we ask that the SRP deny approval of the proposed HDI RELs until our concerns can be sufficiently considered and addressed.

Thank you for considering our comments. If you have any questions or require additional information on any of the comments provided, please do not hesitate to contact me at sahar_osman-sypher@americanchemistry.com or 202-249-6721.

Sincerely,

Sahar Osman-Sypher
Director, Aliphatic Diisocyanates Panel

[1] The Aliphatic Diisocyanates Panel represents the U.S. companies that manufacture or import HDI, HMDI, and IPDI. For more information, visit our website at www.americanchemistry.com/adi.
[2] OEHHA Response to Public Comments on the Proposed Reference Exposure Levels for Hexamethylene Diisocyanate (Monomer and Polyisocyanates) (HD), Feb 4, 2019: https://oehha.ca.gov/media/downloads/crnr/hdirelsoehharesponsepubcomments020419.pdf
[3] OEHHA Draft RELs for HDI, Feb 4, 2019: Draft Reference Exposure Levels for Hexamethylene Diisocyanate (Monomer and Polyisocyanates) (HDI), Feb 4, 2019: https://oehha.ca.gov/media/downloads/crnr/hdirelssrpreviewdraft020419.pdf

AMERICAN CHEMISTRY COUNCIL
ALIPHATIC DIISOCYANATES PANEL

COMMENTS ON
CALIFORNIA OFFICE OF ENVIRONMENTAL HEALTH HAZARD PROPOSED REVISED REFERENCE EXPOSURE LEVELS FOR HEXAMETHYLENE DIISOCYANATE (MONOMER AND POLYISOCYANATES)

Comment 1

OEHHA used a 3-week exposure study to derive the acute HDI monomer REL. We believe the Kopf (2015) 1-week HDI exposure study is a more appropriate surrogate for acute exposures.

As stated by OEHHA in the write-up for the HDI Monomer Acute Reference Exposure Level (REL), the acute RELs are levels at which infrequent one-hour exposures, no more than once every two weeks, are not expected to result in adverse health effects. OEHHA used repeated exposure studies for the derivation of the No Observed Adverse Effect Level (NOAEL) for the acute REL. The Shiotsuka et al. (2006) study involved a 3-week exposure for 5 hours/day for 5 days/week. This study demonstrated increased squamous metaplasia and goblet cell hyperplasia in the anterior portions of the nose at 0.005 ppm, which the study authors considered to be a "subtle adaptive epithelial response to injury". The study authors set the NOAEL to 0.0175 ppm. OEHHA used the No Observed Effect Level (NOEL) of the study (0.005 ppm) as the NOAEL in its derivation of the acute REL.

In response to the original comments submitted by ACC, OEHHA stated that epithelial changes including increased squamous metaplasia and goblet cell hyperplasia to the respiratory epithelium have been used by OEHHA as the basis of 8-hour/chronic RELs for acrolein. This is reasonable given that the effect is a response to repeated exposure to an irritant chemical. However, the response would not occur following the "infrequent one-hour exposures" that the acute REL is designed to protect against. It is more appropriate to use the stated NOAEL of the study when assessing effects expected for only acute 1 hour exposures. Therefore, we feel the HDI Monomer Acute REL should be calculated using the NOAEL of 0.0175 ppm. The lack of adverse effects at this concentration following 3 weeks of repeated exposure is already a conservative protection for "infrequent one-hour exposures". Additional protection for cumulative effects that occur only following repeated exposures is unnecessary when calculating an acute REL.

A more appropriate study for calculation of the acute monomer REL is the Kopf (2015) 1-week exposure study conducted on HDI monomer, which is available on the ECHA website (https://echa.europa.eu/registration-dossier/-/registered-dossier/14852/7/6/3/?documentUUID=e000ffca-52b7-497f-a0f8-8f16072bbc4f). In the 1-week study, rats were exposed to HDI for 6 hours/day, 5 days/week for 1 week to concentrations of 0.027, 0.1, 0.46, and 1.97 ppm. According to the summary, rats exposed to 0.1 ppm did not display any substance-specific clinical signs. They displayed minimal (if any) changes in lung

function and histopathology at 0.1 ppm. Histopathology revealed the typical anterior-posterior gradient of irritation related injury in the nasal cavity at the two highest doses. Animals exhibited reflexively-induced changes in breathing patterns due to stimulation of the nociceptive trigeminal nerve located in the nasal cavity. The study author determined that 0.1 ppm constituted the borderline NOAEL based on effects observed in the upper respiratory tract. The NOEL of the 1-week study is 0.027 ppm. A health protective selection of the NOAEL, such as preferred by OEHHA, would set the NOAEL in the 1-week study at 0.027 ppm. We believe use of the 1-week HDI exposure study provides a better surrogate for acute exposures than the 3 week study. A robust summary of the 1-week study has been provided as part of these comments and the full study is available upon request.

If OEHHA choses to continue using the Shiotsuka (2006) study to derive the point of departure for the acute HDI monomer REL, the 1-week study should be used as evidence that 0.005 ppm is not the appropriate NOAEL from which to derive the REL. The more appropriate NOAEL from which to derive a REL for infrequent 1-hour exposures is 0.0175 ppm.

Comment 2

OEHHA has incorrectly stated that there are no C x T studies for HDI. For the time extrapolation, we believe n=1 is the correct exponent to use in Haber's law.

In response to ACC's previous comments, OEHHA reevaluated their decision for using "n"=1 for the HDI monomer acute REL. They determined that there was not enough evidence to assume equal dependence on concentration and exposure duration in extrapolating from a 5-hour exposure to a 1- hour exposure. Therefore, the HDI monomer acute REL was revised using the default "n"=3 for time extrapolation. In support of this decision, OEHHA stated that no C x t study has been conducted for isocyanates, other than MDI.

It is incorrect that there are no C x t studies conducted on isocyanates. C x t studies have been conducted on TDI and HDI (Pauluhn 2014 and Pauluhn 2015). The rationale for C x t using these isocyanates, as well as the difference in C x t study protocols for aerosol versus vapor is detailed in North et al. (2016). Pauluhn found that both concentration and time can be used to achieve the desired pulmonary dose, but that different exposure designs are best suited for aerosols and reactive vapors. For aerosols such as MDI and HDI polyisocyanates, a variable Concentration x constant Time challenge protocol is best suited to quantify the lower respiratory tract irritation dose. Reactive vapors, such as TDI and HDI, are better suited to the use of a constant Concentration x variable Time protocol.

The physicochemical properties of HDI-vapor favor its retention in the upper airways (Schroeter 2013, Shiotsuka 2006, 2010). For reactive vapors, such as HDI to achieve the desired pulmonary dose, the concentration selected must be high enough to overcome the scrubbing capacity of the nasal passages in obligate nasal breathing rats, while being low enough to minimize irritation induced stimulation of the trigeminal nerve and reflex depression in breathing rate. In Pauluhn 2015, pre-studies in the HDI C x t study were conducted using

equally spaced priming/aggravation inhalation exposures to mildly alveolar irritating concentrations of HDI at durations long enough to deliver a sufficiently high inhaled dose (C x t) of HDI to the distal airways of the lung. Pauluhn found that both concentration and time could be used to achieve the desired pulmonary dose. However, the exposure regime employed by Pauluhn was designed to provide the most conclusive results and overcome the physiological differences between human and rodents. Therefore, if Haber's law is used for time extrapolation of the NOAEL derived from the Shiotsuka (2006) study, n=1 is the correct exponent to use.

However, according to the *OEHHA Technical Support Document for the Derivation of Noncancer Reference Exposure Levels (TSD)*, Haber's Law does not apply to trigeminal irritation effects. In the TSD on page xiii, OEHHA stated that they will not use Haber's Law adjustments for instances in which a trigeminal mechanism for eye, nasal, and respiratory irritation can be determined for the chemical and concentration of concern. The 1-week study on HDI states that the effects which occur at low doses (0.027 and 0.1 ppm) are signs of respiratory tract irritation including changes in breathing patterns, which originated from stimulation of the nociceptive trigeminal nerve located in the nasal cavity. Use of the more appropriate 1-week study to set the acute HDI monomer REL would eliminate the need for the Haber's law adjustment.

Comment 3

We believe the subchronic uncertainty factor that OEHHA applied to the HDI Polyisocyanate 8-hour REL is unnecessary based on OEHHA's own guidance.

According to *OEHHA's Technical Support Document for the Derivation of Noncancer Reference Exposure Levels*, this factor only applies to Chronic RELs. Please see the information below, which was taken directly from the Guidance document. Page 48-49 shows that the subchronic uncertainty factor applies only to chronic studies.

TABLE 4.4.1. POSSIBLE DEFAULT UNCERTAINTY FACTORS USED IN DERIVING ACUTE, 8-HOUR AND CHRONIC RELS

Subchronic uncertainty factor (UF_S)		
Method or Factor	***Values Used***	***REL types***
Values used:	1 Study duration >12% of estimated lifetime √10 Study duration 8-12% of estimated lifetime 10 Study duration <8% of estimated lifetime	C

The removal of the uncertainty factor, which according to the OEHHA guidance document is not necessary for the 8-hour REL, would result in total uncertainty factors of 600
(Total UC: 2 x 3 x 10 x10 = 600)

With this correction made, the final HDI Polyisocyanate 8-hr REL should be 1.5 $\mu g/m^3$ and not 0.8 $\mu g/m^3$.

HEC 1.07 x 0.84 = 0.9
REL 0.9/600 = 1.5 $\mu g/m^3$

Comment 4

There is a typo in the NOAEL for the HDI monomer 8-hour REL.

The NOAEL currently reads 0.1.23 ppb and should read 1.23 ppb.

Comment 5

The HDI monomer acute REL is unnecessarily overly conservative for the reasons articulated below.

Evidence 1:
In the TDI REL, OEHHA stated that the acute TDI REL is 3-fold lower than the NOAEL upon which the 8-hour and chronic RELs rely on as the point of departure for REL derivation. They determined that the TDI acute REL was reasonably protective against sensitization under a scenario of infrequent exposures. In the case of the HDI, the acute REL is more than 100-fold lower than the study relied upon for the 8-hour and chronic RELs.

Evidence 2:
In the TDI REL, OEHHA compared the human worker exposure level derived by Pauluhn for respiratory tract irritation and prevention of sensitization (Pauluhn 2014) to its derived REL. The OEHHA-derived comparison acute REL for TDI was 16.7 $\mu g/m^3$ (2.4 ppb). The REL derived by OEHHA was 8-fold lower and determined to be sufficiently health protective.

Following the rationale in the TDI REL, a comparison of the acute REL for HDI with the human worker exposure level derived by Pauluhn can also be conducted. In this comparison, the rat respiratory tract irritation/sensitization threshold of 900 mg/m^3 x min derived by Pauluhn is divided by 60 minutes to determine a concentration of $15mg/m^3$ as the point of departure. From the TDI REL documentation, it would be expected that OEHHA would apply the dosimetric adjustments developed by Pauluhn (2015) of 3 for obligate vs. oronasal breathing and 3 for the assumption that a human may not depress their respiration rate and minute volume as rats do with exposure to irritant doses of HDI. Along with these interspecies toxicokinetic adjustments, in the TDI comparison, OEHHA included a default interspecies toxicodynamic uncertainty factor of 3 and an intraspecies uncertainty factor of 30 (10 for toxicokinetic and 3 for toxicodynamic

for variability in the human population, not just a worker population). Inclusion of the same uncertainty factors in the HDI comparison would result in a total uncertainty factor of 1000 (3 x 3 x 3 x 3 x 10). The comparison REL for HDI is 0.015 mg/m^3 (15 μg/m^3). The REL derived by OEHHA when setting the LOAEL from the Shiotsuka (2006) study as the NOAEL is 0.3 μg/m^3, which is 50-fold lower.

Evidence 3:

Test chamber studies failed to demonstrate changes in breathing function or bronchial reactivity after exposure to an approximate total HDI dose of 100 μg. Brorson et al. (1990) exposed five male subjects to HDI for 7.5 hours. The average air concentration was approximately 25 μg/m^3 and the total inhaled dose of HDI per subject was estimated to be 100 μg. The subjects had normal vital capacity and FEV1 and did not show signs of bronchial reactivity. In addition, there were no changes in spirometry or bronchial reactivity immediately or 15 hours after exposure. The authors believed that the absence of symptoms and unchanged bronchial reactivity after provocation indicated that exposure to HDI concentrations used in the chamber test did not pose any serious harm to the mucous membrane of the respiratory tract of the subjects.

REFERENCES

California Environmental Protection Agency (2008) Air Toxics Hot Spots Risk Assessment Guidelines: Technical Support Document for the Derivation of Noncancer Reference Exposure Levels. Oakland, CA.

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Shiotsuka RN, Stuart BP, Charles JM, Simon GS, Malichky P and Mostowy JM (2010). Chronic inhalation exposures of Fischer 344 rats to 1,6-hexamethylene diisocyanate did not reveal a carcinogenic potential. Inhal Toxicol 22(10): 875-87.

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.

ATTACHMENT:

Robust Summary for Kopf (2015) HDI 1-Week Subacute Pilot Inhalation Study in Wistar Rats

4. SUMMARY

A repeated exposure 1-week subacute inhalation study with the HDI-vapor, hence-forward referred to as *test substance,* was conducted in young adult male Wistar rats. The procedures called for by OECD-GD#39 (2009) and OECD#412 (2009) were closely observed.

Study design: Wistar rats were nose-only exposed (exposure: 6-hrs/day, exposure on 5 days/week for 1 week to mean actual concentrations of 0.027, 0.1, 0.46, and 1.97 ppm (Note: The concentrations of test atmosphere given are based on breathing zone concentrations from nitroreagent-derived analyses which reflect those measurements performed real-time by FT-IR). Five rats per core group were allowed to recover during a 6-week postexposure period. Additional 5 male rats/satellite group were subjected to lung function measurements on exposure days 0 (nor prior exposure to HDI) and 4 (4 prior exposures to HDI). The exposure took place in directed-flow nose-only inhalation chambers, duration 6 hours/day. Lung function measurements were made in volume displacement plethysmographs (during exposure). The conventional endpoints (clinical observations, body temperature, body weights, food/water consumption, gross necropsy, organ weights, histology) were also evaluated in main group animals. At each sacrifice (3 days and 6 weeks post-exposure period), the weights of the lungs and lung associated lymph nodes were determined. The entire respiratory tract was examined by light microscopy in all main group rats.

Results: The rats exposed up to 0.1 ppm did not display substance-specific clinical signs, hypothermia or conclusive changes in body weights, and food/water consumption. Minimal (if any) changes in lung function and histopathology occurred at 0.1 ppm. Rats exposed at 0.46 and 1.97 ppm displayed signs of upper respiratory tract (sensory) irritation which included irregular breathing patterns, bradypnea, labored breathing pattern, dyspnea, breathing sounds, stridor, nasal discharge (serous), nose/muzzle red encrusted, nostrils red encrusted, motility reduced, atony, high-legged gait, piloerection, haircoat ungroomed before exposure, cyanosis, emaciation, hypothermia, decreased body weights and food/water consumption. There were no statistically significant or conclusive changes in absolute or relative organ weights up to 1.97 ppm.

Evidence of upper respiratory tract sensory irritation occurred at 0.46 and 1.97 ppm on day 0 with increased susceptibility evidenced by a borderline decrease of reflexively-induced bradypnea at 0.1 ppm. The sensory irritation decrease in respiration of rats exposed at 0.46 and 1.97 ppm was essentially identical on day 4. Thus, time-related exacerbation between days 0 and 4 occurred at 0.46 ppm only with reproducible changes at 1.97 ppm. The decrease at this level was in the range

of 40-45% of the air-exposed control. There was no evidence of adaptation of tolerance that would had decreased the susceptibility of animals to sensory irritation due to loss of nerve function.

Histopathology demonstrated irritation-related changes in the larynx, a minimal or slight epithelial metaplasia, coexisting with minimal epithelial alteration and inflammatory infiltrates, were observed at 1.97 ppm. Due to the borderline intensity of finding they are not considered to be of particular significance based on the interpretation of Kaufmann et al. (2009) and relative to those occurring in the nasal cavities. In the lungs of rats exposed at 1.97 ppm enlarged and/or foamy alveolar macrophages, partly with brownish cytoplasm, were observed in the absence of inflammatory changes. This is taken as indirect evidence of stimulated upper airway reflexes and associated vagal stimulation. The resultant cardiopulmonary physiology may have affected the fluid-balance of the lung consistent with the type of changes observed.

The target structures of HDI vapor were confined to the nasal cavities. In the dorsal medial meatus a typical anterior-posterior gradient of irritation and tissue injury occurred at 0.46 ppm relative to 1.97 ppm. At these exposure levels evidence of increased BALT (bronchus associated lymphoid tissue) existed. Subepithelial persistent neurodegeneration was unequivocally apparent at 1.97 ppm with borderline and partly reversible changes at 0.46 ppm. An inconsiderable onset of subepithelial neurodegeneration seems to have occurred at the 0.1 ppm exposure level. The S-100 proteins are a family of low-molecular-weight proteins normally present in cells derived from the neural crest (Schwann cells, melanocytes and glial cells), chondrocytes, adipocytes, myoepithelial cells, macrophages, Langerhans cells, dendritic cells, and keratinocytes. S100 proteins have been implicated in a variety of intracellular and extracellular functions, *inter alia*, Ca^{2+} homeostasis, the dynamics of cytoskeleton constituents, enzyme activities, cell growth and differentiation, and the inflammatory response and are used as cell markers for anatomic pathology. In the light of the inflammatory changes, including subepithelial edema, the neurodegeneration seen in these groups seems to be a logical sequel to inflammation. S100 staining supplements this interpretation. Collectively, rats exposed at 0.46 and 1.97 ppm showed minimal to moderate graded epithelial lesions as well as turbinate remodeling with borderline (if any) response at 0.1 ppm.

In summary, this study did not reveal evidence of pulmonary or thoracic airways irritation. Histopathology revealed and reproduced the typical anterior-posterior gradient of irritation-related injury in the nasal cavities at 0.46 and 1.97 ppm. Reflexively-induced changes in breathing patterns originate from stimulation of nociceptive trigeminal nerve located in the nasal cavity. Functionality of nerves is

evidenced by reflexively-induced bradypnea. Attenuation of reflexes ("tolerance") is taken as robust, integrated physiological evidence of nerve function. Collectively, physiological measurements did reveal increased responsiveness at 0.46 ppm and unchanged responsiveness at 1.97 ppm from measurements made on exposure days 0 and 4. Histopathology showed neurodegeneration in conjunction with inflammation and subepithelial edema in the nasal cavities especially at 0.46 and 1.97 ppm. The integrated quantitative physiological measurement takes precedence over the semi-quantitative pathological analyses at selected anatomical sites of the nasal cavities. Taking all findings into account, 0.1 ppm constitute the borderline no-observed-adverse-effect-level (NOAEL) based on the effects observed in upper respiratory tract effects.

S.