Responses to Public Comments on the Draft Reference Exposure Levels for Hexamethylene Diisocyanates (Monomer and Polyisocyanates)

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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On December 1, 2017, the Office of Environmental Health Hazard Assessment (OEHHA) released the draft document, *Hexamethylene Diisocyanate Reference Exposure Levels (Monomer and Polyisocyanates): Technical Support Document for the Derivation of Noncancer Reference Exposure Levels* to solicit public comments. Responses to comments received on the draft hexamethylene diisocyanate (HDI) reference exposure levels (RELs) are provided here.

Background

The Office of Environmental Health Hazard Assessment (OEHHA) is required to develop guidelines for conducting health risk assessments under the Air Toxics Hot Spots Program (Health and Safety Code Section 44360(b)(2)). OEHHA developed a Technical Support Document (TSD) in response to this statutory requirement that describes acute, 8 hour and chronic RELs and was adopted in December 2008. The TSD presents the methodology for deriving RELs. In particular, the methodology explicitly considers possible differential effects on the health of infants, children and other sensitive subpopulations, in accordance with the mandate of the Children's Environmental Health Protection Act (Senate Bill 25, Escutia, Chapter 731, Statutes of 1999, Health and Safety Code Sections 39669.5 *et seq.*). These guidelines have been used to derive separate sets of new acute, 8-hour and chronic RELs for HDI monomer and for HDI-based polyisocyanates.

Comments on the Draft RELs for HDI (monomer and polyisocyanates) were received from:

- American Chemistry Council (ACC) Aliphatic Diisocyanates Panel

Responses to Comments Received from ACC

ACC Comment 1:

"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."

Response to ACC Comment 1:

OEHHA recognizes that the manufacture of HDI monomer is in closed systems with little or no potential exposure to the general public. However, exposure to HDI monomer gas and HDI-based prepolymers may occur due to emissions of HDI-based spray paint. The limited data for area exposures near spraying booths show low levels of polyisocyanates, but can be above the proposed OEHHA RELs (Myer *et al.*, 1993). Exposure to microgram per cubic meter ($\mu g/m^3$) levels of HDI polyisocyanates can result in acute and chronic injury. The concern for exposure therefore is focused on automotive spray painting facilities in California. As reported in Section 9 of the HDI REL document, it has been estimated that there are about 35,000 automotive refinishing facilities in the US (Sparer *et al.*, 2004; Woskie *et al.*, 2004). If California's share is around 12 percent of these (roughly the percentage of the US population), that could mean the state has up to 4200 facilities that are involved in using HDI-based polyisocyanates for spray painting or some other process. It has also been estimated

that there are 125,000 auto body painters in the US (Cullen *et al.*, 1996). Again, assuming California's share is 12 percent, this would mean there are 15,000 auto body painters in California. OEHHA believes the potential exists for exposure to HDI-based spray paint emissions, even if there are currently no published reports documenting serious exposure to the general public.

Regarding exposure to the volatile HDI monomer, OEHHA also recognizes that the risk posed by the monomer is going to be lower compared to the risk posed by HDI prepolymers. HDI-based spray paints are documented as usually consisting of less than 1 percent of the HDI monomer. Research in animals indicates that HDI monomer levels up to 2 percent in HDI-based polyisocyanate mixtures has no additional toxic effect over what was found for the prepolymer(s) in the formulation (Pauluhn, 2008). In other words, the HDI polyisocyanate RELs accounts for the residual content of monomeric HDI as long as it is at or below 2 percent. Thus, OEHHA states in Section 9.6 of the REL document that "For any HDI-based polyisocyanates with a monomeric HDI content above 2%, it is recommended that exposure for the monomer be assessed separately."

However, the HDI monomer level can increase in the paint, depending on duration of storage and temperature during storage (Myer *et al.*, 1993). Also, some painting processes suggest breathing zone levels of HDI monomer could reach as high as 10 percent of total HDI-based polyisocyanates (Akbar-Khanzadeh and Rivas, 1996). In another study of automotive spray paint products and task-based spraying methods, breathing zone levels of HDI monomer can reach well above (maximum 179 $\mu g/m^3$; 26 parts per billion [ppb]) the proposed REL values in this TSD (Fent *et al.*, 2008).

Thermal decomposition of HDI-based polyisocyanates coatings will release HDI monomer, depending on the temperature of the fire. Heating of car paint samples have resulted in release of 3.58 mg/g of degraded polymer (Boutin *et al.*, 2005). In addition, low $\mu g/m^3$ levels of HDI and isocyanates have been measured in air during grinding and welding processes in auto repair shops (Karlsson *et al.*, 2000; Henriks-Eckerman *et al.*, 2002).

Overall, OEHHA believes there is the potential for exposure to HDI monomer and prepolymers in polyisocyanate mixtures that could represent a health risk, necessitating the need for health values to assess the noncancer hazard.

ACC Comment 2:

"Exposure: 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."

Response to ACC Comment 2:

The US EPA project the ACC is referring to was undertaken in 2009-2010. Key monitored pollutants varied among the schools, based on background information on potential pollutants emitted near the schools. Of the 62 schools investigated, six of the schools were monitored for diisocyanates, sometimes in conjunction with other unrelated pollutant sources. Some of these six schools had been ranked in the top 25 on a list compiled by USA Today for potential diisocyanate emission impacts. The findings were based on 2005 Toxics Release Inventory (TRI) data. The report by USA Today appears to be what led to the US EPA schools study. US EPA does not appear to have produced an overall summary of the findings at the 62 schools. Rather, US EPA's website contains short individual reports on each school at https://www3.epa.gov/air/sat/index.html

The facilities emitting diisocyanates near schools included a consumer product packaging plant, a coatings facility, a door manufacturing facility, a plastics manufacturing facility, a rubber and plastics facility, and a boat manufacturer. Air monitoring was performed for HDI, MDI and TDI, which are found primarily in gas form. At four of the six facilities, only MDI or TDI was emitted. The other two facilities were reported to release HDI, MDI and TDI, but it was unclear from these reports which diisocyanate(s) predominated. Sampling days included some measurements when meteorological conditions favored wind patterns blowing emissions towards the schools.

A low-volume portable air sampling pump was used, in which the sampling medium was glass fiber coated with 1-(2-pyridyl)piperizine. 1-(2-pyridyl)piperizine is a derivatizing reagent that forms a nonvolatile derivative in reaction with isocyanate groups. The sampling duration was 4 sequential samples, each of 5 hours duration over a 24 hour period. The monitor collects samples usually over 60-90 days and takes air samples on at least 10 different days during that time. The average method detection limit varied slightly depending on the site. For HDI the detection limit was as low as 0.309 $\mu g/m^3$. For MDI and TDI, the average detection limit was between 0.143 and 0.190 $\mu g/m^3$.

As noted by ACC, US EPA detected no diisocyanates at any of the six schools. The lack of findings was a result of one or more of the following reasons, as cited by US

EPA in the individual school reports: significant over-reporting of diisocyanate emissions to the TRI, significant reductions in emissions by the time monitoring was implemented, emissions that were already below the reportable threshold, and facility operations that were significantly below 100% of capacity at the time of monitoring. Distance between the schools and individual diisocyanate emission sources, when reported, ranged from 0.6 mi. to 1.5 miles. The schools may have been too far from the facilities for emissions to reach them in quantifiable amounts.

The US EPA findings suggest to OEHHA that, for the various reasons discussed above, these schools may not have been the ideal locations to monitor for residential impacts of diisocyanate emissions. No fenceline monitors were installed just outside of facility boundaries, and no residences closest to the facilities were monitored. Regarding HDI, only two facilities potentially emitted this compound and it was unclear if HDI monomer or prepolymers (or both) were involved. The collection system used, reagent-coated glass fiber filters, are able to collect diisocyanate vapors and particles of widely varying sizes (NIOSH, 1998; Marand *et al.*, 2004). However, detection was apparently limited to only the diisocyanate gases, and therefore any HDI prepolymers or oligomers present in air may have been missed.

In summary, the US EPA sampling of schools was inadequate to support a conclusion that diisocyanates are not an air pollutant of concern for the general population.

ACC Comment 3:

"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”

Response to ACC Comment 3:

As described in the OEHHA REL summary, Shiotsuka et al. (2006) observed squamous metaplasia, epithelial hyperplasia and goblet cell hyperplasia that was statistically significantly increased ($p<0.05$) at 0.005 ppm HDI in the nasal epithelium of the post-incisor region. The histopathologic changes in rats exposed to 0.005 ppm (squamous metaplasia, epithelial and goblet cell hyperplasia) were considered by the authors to be reversible tissue changes and not adverse in nature. Cellular proliferative changes were stated by the authors to reflect a reparative or adaptive compensatory process and not necessarily a progression to an adverse effect.

As described in the OEHHA REL summary in Section 9.1, “…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, another respiratory airway irritant gas.” OEHHA considers cellular responses caused by the irritant action of a known chemical irritant to represent an adverse effect for acute REL derivation purposes.

As noted in the REL summary, other multi-day exposure studies (continuous exposure for 19 days, and up to 49 days discontinuously) did not find nasal epithelial changes in the post-incisor region of rats following exposure to 0.005 ppm HDI, but observed significant changes at the next highest dose of 0.05 ppm (Astroff *et al.*, 2000a; Astroff *et al.*, 2000b). However, some possible effects (non-significant acanthosis and inflammation) in the more anterior vestibule region were observed at 0.005 ppm (Astroff *et al.*, 2000a). Based on the Astroff studies, a Point of Departure (POD) of 0.005 ppm (the NOAEL) would also be used for REL derivation by OEHHA staff.

Thus, OEHHA does not believe using a single 5 hour exposure to 0.005 ppm as a point of departure, based on findings after three weeks of exposure, is overly conservative. OEHHA modified a sentence in the REL summary (Section 9.1) to state this more clearly, “Based on these results from the 3-week multi-day exposure study, which suggest a near-threshold response at 0.005 ppm, OEHHA chose a health-protective approach by using a single 5-hr exposure to 0.005 ppm (0.034 mg/m^3) as the point of departure for acute REL derivation.”

ACC Comment 4:

"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/m^3
HEC 6.6 x 0.45 = 2.97 mg/m^3
REL 2.97/200 = 14.8 ug/m^3"

Response to ACC Comment 4:

The data used as the basis for making the "n" = 1 determination for use in the modified Haber's Law equation ($C^n \times t = K$) was derived from a C × t study with polymeric MDI (Pauluhn, 2002). In this study, concentration (C) and time (t) were varied in a way that always equaled the same C × t product. For example, if doubling the exposure duration and reducing the concentration by half resulted in the same quantifiable toxic effect, then "n" is equal to one. Thus, the toxic response is equally reliant on concentration and exposure duration. Pauluhn (2002) observed that "n" is equal to one for PMDI for a sensitive indicator of pulmonary injury in rats: increased total protein in bronchoalveolar lavage fluid.

Unfortunately, no C × t study has been conducted for other isocyanates, including HDI monomer and prepolymers. Pauluhn (2015) did conduct a study in which "t" was varied, but it was not a true C × t study. Because no C × t study has been conducted for HDI-based prepolymers, the health protective default "n" = 3, as discussed in the OEHHA Noncancer Guidelines (OEHHA, 2008), is used in the Haber's Law equation.

This comment caused OEHHA staff to reassess the decision for using "n" = 1 for the HDI monomer acute REL. The decision was that not enough evidence exists to assume equal dependence on concentration and exposure duration in extrapolating from a five hour exposure to a one hour exposure. Therefore, the HDI monomer acute REL was revised using the default "n" = 3 for time extrapolation.

The revised paragraph in Section 9.1 of the REL summary states, "A time extrapolation from a 5-hr exposure to 1 hr was used applying the modified Haber's Law $C^n \times t = K$ with a default "n" = 3. The resulting time-adjusted POD is 0.00588 mg/m^3 for a 1-hour exposure. Haber's Law states that the product of the concentration (C) and time of exposure (t) required to produce a specific physiologic effect are equal to a constant level or severity of response (K). When "n" is not known, a modified version of Haber's Law is used for extrapolation (i.e., "n" = 3) when adjusting an exposure duration of greater than 1 hour to 1 hour. This health protective approach assumes concentration is the main driver for acute effects, rather than exposure duration. The C × t studies for PMDI showed an equal dependence on changes in concentration and duration of exposure ("n" = 1) for acute effects in the pulmonary region (Pauluhn, 2002). However, a similar C × t study has not been performed for HDI."

This revision for HDI monomer reduced the acute REL from 0.9 µg/m^3 to 0.3 µg/m^3.

ACC Comment 5:

"8 Hr and Chronic HDI Monomer REL: The 8 hr 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"

Response to ACC Comment 5:

In 1994, before the publication of peer-reviewed occupational studies by Cassidy et al. (2010) and Hathaway et al. (1999), US EPA (1994a) based its RfC on chronic HDI exposure in rats. The critical endpoint was nasal olfactory epithelium degeneration, in which the point of departure was a NOAEL of 5 ppb (35 µg/m^3). Following time adjustment, application of the Human Equivalent Concentration (HEC), and use of a total uncertainty factor of 100, the RfC was 0.01 µg/m^3 (0.0016 ppb). The RfC of 0.0016 ppb is lower than the chronic REL based on human exposure derived by OEHHA (0.004 ppb).

There are no peer-reviewed human exposure studies that established an occupational Threshold Limit Value - Time-Weighted Average (TLV-TWA) of 5 ppb. OEHHA cannot use apparent anecdotal evidence of an occupational threshold limit of 5 ppb. OEHHA staff used peer-reviewed occupational studies to determine a point of departure of 1.23 ppb. This concentration represents the 90th percentile of the 237 samples collected by Cassidy et al. for their estimation of occupational exposure. The data was kindly provided by Dr. Cassidy, which was obtained following release of the Public Review version of the HDI REL summary. OEHHA staff used the exposure data to calculate the distribution from which a more relevant POD was selected. This changed the POD of 0.78 ppb in the Public Review version, to 1.23 ppb in the current version of the HDI REL summary.

With the publishing of these relatively recent occupational studies, OEHHA staff did not have to rely on a chronic rat study for the point of departure. As noted in the REL summary, OEHHA staff found the retrospective occupational study by Cassidy et al. (2010) to provide the highest 8-hr TWA mean HDI concentration (13.5 yr exposure duration, n = 100 workers) that did not result work-related respiratory problems or lung function deficits compared to matched controls. In addition, the study provided the most comprehensive information on TWA occupational exposure to HDI in workers not wearing protective respiratory equipment. Using an animal study for the REL would have added additional uncertainty factors for extrapolation from animal exposure to human exposure and would have resulted in an overly conservative REL. In addition, some differences between rats and humans in modeled regional airway deposition of inhaled HDI by Schroeter et al. (2013) suggests that rats may not be the best model to use for human exposure to HDI.

ACC Comment 6:

"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/m^3 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 µg/m^3 and not 0.8 µg/m^3.

HEC 3.214 x 0.84 = 2.7
REL 2.7/600 = 4.5 µg/m^3"

Response to ACC Comment 6:

There were no errors in calculating the 8-hour REL for HDI-based polyisocyanates.

First, for the time adjustment of the POD (3 mg/m^3), OEHHA staff used the equation:

3 mg/m^3 × 6/24 hrs × 5/7 days × 20/10 m^3

To calculate the time adjustment based on a 6-hour animal exposure, exposure time is first adjusted to a continuous, daily exposure – 6 hrs / 24 hrs × 5/7 days – just as in calculating the chronic REL. To then adjust for the 8-hour REL, the 20 m^3 / 10 m^3 factor is used because half the air breathed in a day occurs during the active 8-hour work period (when exposure to pollutants occur). Given that humans breathe approximately 20 m^3 of air per day, the 8-hour daily working period will result in 10 m^3 of air breathed because of the greater activity and respiratory rate during this period. If both the 8-hour and chronic RELs are based on the same study, the result is that the 8-hour time-adjusted POD will be twice that of the chronic time-adjusted POD.

OEHHA has used this time adjustment (6/24 hrs × 5/7 days × 20/10 m^3) for other 8-hour RELs based on animal studies, including MDI, acrolein and acetaldehyde.

We state in our acetaldehyde REL derivation (OEHHA, 2008, Appendix D1) that:

"The time adjustment for an 8-hour REL used is 6h/24h × 20 m^3/10 m^3, rather than 6 h/8 h, because we assume that the 8 hours includes the active waking period when an adult inhales 10 m^3 of air, i.e. half the daily total intake of 20 m^3."

Second, regarding use of a subchronic uncertainty factor for the 8 hour REL, the 8-hour REL is similar to the chronic REL in that both are to protect humans from long-term exposures to toxicants. The 8-hour REL is for daily 8-hour exposures, and the chronic REL is for continuous, 24-hour exposure, so the subchronic uncertainty factor also applies to the 8-hour REL.

ACC Comment 7:

"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."

Response to ACC Comment 7:

For the acute, 8-hour and chronic HDI-based polyisocyanate RELs and acute HDI monomer REL, we state in Section 9:

"A default interspecies toxicodynamic $UF_{A\text{-}d}$ of $\sqrt{10}$ is applied to account for use of key studies employing non-primate species and the lack of data for toxicodynamic interspecies differences."

A default interspecies toxicodynamic (TD) UF of 3 (also expressed as $\sqrt{10}$) is applied when there is no data on TD interspecies differences, whether or not the chemical is a direct or indirect acting agent on respiratory epithelial tissue. This is consistent with our default uncertainty factor approach used in deriving RELs (OEHHA, 2008). The

application by OEHHA of a TD UF = 3 can also be found in the derivation of other RELs in which the critical endpoint is olfactory or respiratory epithelial lesions in rodent species, including acetaldehyde, acrolein, MDI, and others.

In addition, the ACC statement that "*HDI monomer and HDI polyisocyanates are direct, local acting toxicants with no systemic effects*" is not entirely true. Numerous studies have observed HDI hemoglobin and protein adducts in the bloodstream (Redlich *et al.*, 1997; Wisnewski and Redlich, 2001; Flack *et al.*, 2010; Flack *et al.*, 2011). When inhaled, glutathione-HDI adducts form at the site of contact in the lung lining fluid, and are then shuttled through the body in a reactive form, and subsequently conjugate to proteins distant from the lungs. Although it is unclear if these adducts have a demonstrable toxic action in the body, it would be inappropriate to assume systemic exposure to these adducts have no influence on the development of isocyanate-induced asthma or other diseases.

ACC Comment 8:

"Uncertainty Factors That Apply to Multiple RELs: 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."

Response to ACC Comment 8:

The pathogenesis of isocyanate-induced asthma is a complex process and still largely unknown. However, isocyanates or their metabolites may react with intracellular glutathione (GSH), either directly or after catalysis by the GSTs. Thus, GSTs may help facilitate the reaction of GSH with HDI. Piirila et al. (2001) notes that enzymes of the glutathione S-transferase (GST) supergene family can utilize a wide variety of products of oxidative stress as substrates and are thus critical in the protection of cells from reactive oxygen species (ROS). Exposure to isocyanates causes respiratory symptoms characterized by airway inflammation, eosinophilia, and local formation of ROS. Accordingly, the observed wide genetically-based individual variations in the GST enzyme activities are likely modifiers of susceptibility to isocyanate-induced asthma. Individual capability to tolerate oxidative stress varies, possibly due to genetic factors. Inability to detoxify ROS could therefore lead to inflammatory process, activate bronchoconstrictor mechanisms and cause asthmatic symptoms.

As discussed above and in the HDI REL summary, isocyanates can react with proteins, such as albumin, to form protein conjugates. The protein conjugates may be immunogenic, and the formation of hapten complexes may give rise to immunological reactions. Therefore, in the presence of decreased GSH conjugation related to deficient GST genes, impaired immune response could also be suspected.

In addition to GSTs, a number of other gene variants have been reported to be associated with increased sensitivity to the disease in workers, which suggests that isocyanate-induced asthma represents a complex disease phenotype determined by multiple genes. Examples of genes shown in Table 18 of the OEHHA HDI REL summary include, but are not limited to, genes involved in immune regulation (human leukocyte antigen, cytokines IL4RA, IL-13, and CD14), inflammatory regulation (alpha-T catenin), and other genes involved in antioxidant defense (superoxide dismutase, epoxide hydrolase). The mean Odds Ratios for significant genotype variation associations and increased susceptibility for isocyanate-induced asthma were between 1.89 and 10.36, based on metabolic enzymes including GST, NAT, and EPXH. This would suggest there could be a large (up to 10-fold) variation in the human pharmacokinetic response. Thus, a 10-fold intraspecies toxicokinetic uncertainty factor is appropriate for risk assessment. Further variation in other genes associated with the inflammatory process and immune regulation also demonstrated associations with isocyanate-induced asthma (OR between 2 and 9). Thus, this supports use of a toxicodynamic factor greater than the default of $\sqrt{10}$.

ACC Comment 9:

"Uncertainty Factors That Apply to Multiple RELs: 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."

Response to ACC Comment 9:

The suggestion by the ACC that children may be less sensitive – not more sensitive – to the development of isocyanate-induced lung decrements because it is primarily a Th1 driven pathway in humans is not adequately supported by the available data. It is unknown how children will react to HDI monomer and prepolymer exposure early in life when the immune system is still developing. The development of asthma from exposure to TDI is multifactorial and it is not well understood what the mechanism for isocyanate-induced asthma is in adults, much less children. Uncertainty factors are assigned based on data gaps, and the lack of knowledge regarding the relative

susceptibility of infants and children compared to adults represents a substantial data gap.

The pathophysiology of childhood asthma and isocyanate-induced occupational asthma (in adults) are actually similar. Del Prete et al. (1993) noted that regardless of the differences in T cell profiles, the clinical manifestations and pathophysiological changes observed in isocyanate-induced asthma are remarkably similar to those in atopic asthma. What is unknown is how infants and children would respond to isocyanate exposure during the critical stage of immune system development in the lungs.

Isocyanate-induced asthma studies in adult humans and animal models have shown a selective Th2 type or a mixed Th1/Th2 immune response (Maestrelli *et al.*, 1997; Lummus *et al.*, 1998; Johnson *et al.*, 2007; Kimber *et al.*, 2007). Skin sensitizing chemicals usually induce preferential Th1-type responses. Thus, stating that isocyanate-induced asthma is primarily a Th1 driven pathway represents something of an oversimplification. Isocyanates appear capable of inducing different types of immune reactions, depending on the polarization of the T cells toward the helper T type 1 (Th1) or helper T type 2 (Th2) cells (Ban *et al.*, 2006). In some circumstances, isocyanate-induced asthma may be polarized towards a Th1 pathway. However, the type of T cell response likely depends on exposure conditions including route of exposure (dermal vs. inhalation), the dose of the isocyanate, length of exposure, etc. It also could vary depending on where and when one looks for immune factors (lymph nodes, bronchoalveolar lavage fluid, etc.) and individual genetic difference in susceptibility.

Additionally, childhood asthma may not always show a Th2-driven-type process. Recent research by Youssef et al. (2013) found that obese children with asthma exhibit Th1 polarization, whereas lean children with asthma exhibit Th2 polarization. Their data suggests that in the presence of high leptin levels in the obese children, there is an increase in IFN-γ production by Th1-polarized cells. Leptin is found in higher levels in obese children and is known to promote the production of nitric oxide and pro-inflammatory cytokines in macrophages and monocytes. So, depending on body weight of the child, this research suggests either Th1- and Th2-driven pathways can be involved in childhood asthma. A study by Wei et al. (2011) found that the balance between Th17 cells and regulatory cells is impaired in asthma patients. The Th17 cell is a distinct lineage different from Th1 and Th2 cells, and emerged from the discovery of a new type of cytokine, IL-17. Thus, discussion of primarily Th1- and/or Th2-driven processes in asthma may need to be expanded.

As described in OEHHA (OEHHA, 2001), OEHHA considers asthma to be a disease that disproportionately impacts children. During the prioritization of Toxic Air

Contaminants under the Children's Health Protection Act (SB 25, Statutes of 1999), OEHHA noted that the prevalence of asthma is higher in children, hospitalization rates for asthma are highest in children 0 to 4 years old, and the impact of lost school days and lost activity days dues to asthma uniquely impacts children. Thus, whether there is induction or exacerbation of asthma by isocyanates, there is still a need to include this consideration in our choice of intraspecies uncertainty factors.

ACC Comment 10:

"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."

Response to ACC Comment 10:

Exposure to very low levels (on the order of $\mu g/m^3$) of HDI monomer and polyisocyanates may result in acute and chronic injury, particularly in sensitive individuals. In addition, as many as 4200 facilities in California may be using HDI-based polyisocyanates in spray painting operations or for some other purpose. The high potency plus widespread use of these compounds supports the development of RELs for HDI monomer and polyisocyanates. The type of uses suggest most facilities would only have a small emissions footprint in terms of offsite exposure. However, OEHHA believes the potential exists for near-source exposure to HDI-based polyisocyanate emissions, even if there are currently no published reports documenting serious exposure to the general public.

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