Air Toxics Hot Spots Program

Response to SRP Comments

Draft Noncancer Reference Exposure Levels for

- ***Toluene Diisocyanate (TDI)***
- ***Methylene Diphenyl Diisocyanate (MDI)***

Office of Environmental Health Hazard Assessment

Scientific Review Panel Presentation

August 20, 2015

Toluene Diisocyanate
Preceding SRP Meeting

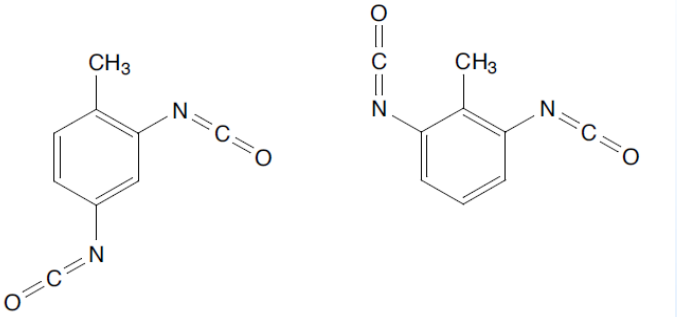
- **At the February 2015 SRP meeting:**
- **Presented draft RELs**
  - **Acute: 2 µg/m3 (0.3 ppb)**
  - **8-Hour: 0.015 µg/m3 (0.002 ppb)**
  - **Chronic: 0.008 µg/m3 (0.001 ppb)**
- **Acute REL based on 10-20 ppb LOAEL – asthmatic response (≥100% increase in airway resistance) in nonsensitized asthmatic subjects**
- **8-hr and chronic RELs based on accelerated lung function decline (FEV1) in 5-year prospective study of TDI workers**

  8-hour time-weighted average in never-smokers:

  NOAEL – 0.9 ppb

  LOAEL – 1.9 ppb

Toluene Diisocyanate (TDI)



2,4-Toluene diisocyanate
CAS No. 584-84-9

2,6-Toluene diisocyanate
CAS No. 91-08-7

- **TDI used in flexible polyurethane foams adhesives and coatings**
- **Global production capacity for TDI exceeds a million tons per year**
- **Volatile: vapor pressure 0.023 mmHg @ 25°C**
- **One of the most potent LMW sensitizers**

Toluene Diisocyanate
Main Revision to the Document

General comment:

- **State more clearly what adverse effects we are trying to prevent with these RELs**

TDI Acute REL
Who Are We Protecting?

Acute adverse effects:

1. **Sensory irritation and respiratory inflammation**
2. **Asthmatic episodes in nonsensitized asthmatics**
3. **Sensitization and induction of TDI-asthma with infrequent acute exposures**
4. **Asthmatic reaction in sensitized individuals**

TDI Acute REL

Sensory/pulmonary irritation in normal subjects

In normal subjects,

- **30 min exposure to 20 ppb and 50 ppb was the NOAEL and LOAEL, respectively, for sensory irritation (eye)**
- **Subjective findings of sensory irritation (eye, cough) at 20 ppb for 2 hrs**
- **Exposure to 5 ppb for 6 hrs followed by 20 ppb for 20 min:**
  - **Decreased s*G*aw (p=0.053) and $MEF_{25\%}$ (p=0.015)**
  - **Increased BALF albumin level (p=0.044) concentration**
  - **Increased BL fluid macroglobulin (p=0.044) concentration**

TDI Acute REL

Asthmatic episodes in nonsensitized asthmatics

SRP Comment:

- **More clearly present the data for increased sensitivity of asthmatics compared to normal subjects**

Referring to studies by Baur and colleagues:

1. **Asthmatics: A significant pulmonary function decrement (>100% increase in Raw) in two of 15 non-sensitized asthmatic subjects exposed to TDI;**

   Normals: Not observed in exposed healthy subjects

2. **An increase in Raw between 50-100% in five additional asthmatic subjects exposed to TDI**

TDI Acute REL

Asthmatic episodes in nonsensitized asthmatics

Continued…

3. **Higher sensitivity of responding asthmatics, relative to others in the study, to non-specific challenge with Ach (<0.1 mg)**

4. **Higher total inhalation dose (i.e., C × t) used compared to most other studies exposing non-sensitized asthmatics to TDI (reason why other studies saw no response)**

5. **Subjective symptoms of chest tightness, rhinitis, cough, dyspnea, throat irritation, and/or headache experienced by several asthmatic subjects from TDI exposure**

Conclusion: There is greater sensitivity to TDI in some asthmatic individuals compared to healthy adults

TDI Acute REL

Sensitization and induction of TDI-asthma

Evidence that infrequent acute (1 hour) exposure at the REL should not result in sensitization:

- **Occupational exposure on the order of months to years leads to sensitization and occupational asthma**
- **No evidence that infrequent exposures as low as proposed REL (0.3 ppb) will result in sensitization**
- **Animal studies indicate the threshold for pulmonary irritation and sensitization are interrelated**
- **Acute REL is 3-fold lower than the NOAEL (0.9 ppb) used as the POD for the 8-hour and chronic RELs**

TDI Acute REL

Can We Protect Sensitized Individuals?

SRP Comments: What is the potential for exposure in individuals already sensitized? Will the acute REL protect these individuals?

1. **OEHHA estimates that only 12 – 43 individuals per million may be sensitized to any diisocyanate**
2. **Most chamber studies to confirm diisocyanate asthma start at 5 ppb and move up step-wise to 10 and 20 ppb, usually 30 min or less per exposure.**
   - **A few studies exposed sensitized individuals to 1 ppb TDI**
   - **Lowest measured was 0.5 µg/m^3 (0.05 ppb) for MDI**

TDI Acute REL

Can We Protect Sensitized Individuals?

Conclusion:

- **The acute REL is lower than the exposures used to test for sensitization**
- **RELs cannot be designed to protect all hypersensitive individuals (in our REL guidance)**
- **Likelihood that the risk of a sensitized individual being exposed to TDI emissions is very low**
- **The acute REL is acceptable for the purposes of the Hot Spots program**

TDI 8-Hr and Chronic RELs

Adverse Effects We Want to Prevent with RELs

8-Hr/Chronic adverse effects:

1. **Accelerated lung function decrements not related to TDI-induced asthma (POD of RELs)**
2. **Sensitization and induction of TDI-asthma**
3. **Asthmatic reaction in individuals previously sensitized to TDI**

TDI 8-Hr and Chronic RELs
Diem et al. Lung Function Study

Diem et al. (1982) report:

Study of accelerated lung function decline (8-hr TWA):

NOAEL: 0.9 ppb

LOAEL: 1.9 ppb

Also stratified workers by time spent below or above 20 ppb:

<0.19 mo exposure to 20 ppb or more – no lung function decline

>0.19 mo exposure to 20 ppb or more – lung function decline

TDI 8-Hr and Chronic RELs
Weill et al. Sensitization/asthma Study

Weill et al. (1981) NIOSH report:

- **Includes study of the 12 "sensitive" workers**
- **Jobs stratified by exposure (8-hr TWA)**

  6.8 ppb (high), 3.2 ppb (moderate), 1.6 ppb (low)

Based on job category:

- **10 sensitive workers in high / moderate exposure groups**
- **2 sensitive workers in low exposure group**
- **6 of these 12 workers were exposed during major spills**

Six sensitive workers went on to become part of a larger chamber exposure study: 2 of these workers were determined to have TDI-asthma

TDI 8-Hr and Chronic RELs

Sensitization and induction of TDI-asthma

Support for 8-hour and chronic RELs protecting against sensitization/asthma:

1. **Acute, subacute and subchronic animal studies indicate the threshold for pulmonary irritation/inflammation and sensitization are interrelated, and fit C × t model**
2. **Reducing exposure reduces prevalence of occupational asthma**
3. **A caveat is that recent studies (Gui et al., 2014) still show a low prevalence of symptoms even in state-of-the-art facilities with very low exposure (0.5-5 ppb during peak hrs); our RELs are considerably lower**

TDI 8-Hr and Chronic RELs

Sensitization and induction of TDI-asthma

Support for 8-hour and chronic RELs protecting against sensitization/asthma continued:

Comment: Uncertainty factors used to derive RELs appear appropriate but need to more clearly present the evidence for the REL derivations

- **evidence of sensitive workers at state-of-the-art facilities**
- **Toxicogenomic data suggest a large variation in response in human population, so we applied a 100-fold intraspecies UF (10-fold UF each for toxicokinetic and toxicodynamic differences)**

TDI 8-Hour and Chronic RELs
Can We Protect Sensitized Individuals?

Can we protect individuals already sensitized to TDI or other isocyanates?

1. **Rough estimate that only 12 – 43 individuals per million may be sensitized to any diisocyanate**
2. **Most chamber studies to confirm diisocyanate asthma start at 1- 5 ppb**
   - **Lowest measured was 0.5 µg/m^3 (0.05 ppb) for MDI**

Proposed 8-hour and chronic RELs are lower than the lowest reported concentration that produced a response in a sensitized individual

8-Hour REL: 0.002 ppb
Chronic REL: 0.001 ppb

TDI 8-Hour and Chronic RELs
Can We Protect Sensitized Individuals?

Conclusion:

- **Our RELs in all likelihood protect sensitized individuals**
- **RELs cannot be designed to protect all hypersensitive individuals (in our REL guidance)**
- **Likelihood that the risk of a sensitized individual being exposed to TDI emissions is very low**
- **The RELs are acceptable for the purposes of the Hot Spots program**

Toluene Diisocyanate
Other Changes to the Document

- **Added "List of Acronyms" at front of document**
- **Added a study that measured emissions of TDI facility stacks, and a non-occupational exposure study resulting in asthma symptoms**
- **Added study summaries on thermal degradation of polyurethane with estimated TDI emissions**
- **Added summaries of mechanistic studies that were recommended for inclusion**
- **Added summary of TDI challenge study by Raulf-Heimsoth et al. (2013) that was recommended for inclusion**

Toluene Diisocyanate
Other Changes to the Document

- **Section added on quantitative analysis methods for airborne TDI**
- **Added summary of TDI occupational study by Gui et al. (2014) that was recommended for inclusion**
- **Added a summary of a consumer product exposure study (emissions and solvent extraction from polyurethane foam)**
- **Added more detail to studies summarized in the Toxiogenomics Section**
- **More clearly specified the specific diisocyanates workers were exposed to in the toxicogenomics studies**

TDI Prepolymers

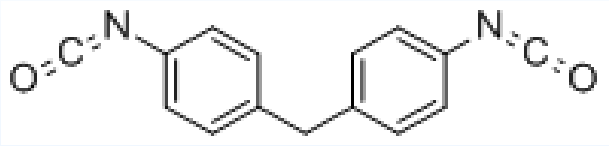
New Section summarizing toxicological studies of TDI prepolymers

- **Very little data on toxicology of TDI prepolymers – insufficient to determine REL values**
- **Most exposures are from TDI monomers**
- **Hot Spots TDI RELs specific for TDI monomers**

Methylene Diphenyl Diisocyanate
Preceding SRP Meeting

- **At the February 2015 SRP meeting:**
- **Presented draft RELs for MDI**
  - **Acute: 12 µg/m^3 (1.2 ppb)**
  - **8-Hour: 0.16 µg/m^3 (0.015 ppb)**
  - **Chronic: 0.08 µg/m^3 (0.008 ppb)**
- **Acute REL point of departure 700 µg/m^3 (68 ppb) LOAEL for PMDI – increased total protein in BALF of Wistar rats**
- **8-Hour REL based on benchmark dose analysis (118 µg/m^3 , 11.5 ppb) for PMDI - bronchiolo-alveolar hyperplasia in Wistar rats**
- **Chronic REL based on LOAEL (230 µg/m^3 , 22 ppb) for MDI - Pulmonary interstitial fibrosis in Wistar rats**

Methylene Diphenyl Diisocyanate (MDI) Reference Exposure Levels



- **Semi-volatile**
- **MDI and polymeric MDI (PMDI) used mainly in rigid polyurethane foams**
- **MDI and PMDI have essentially the same toxicological potencies and endpoints – RELs are relevant to both**

MDI

Main Revision to the Document

General SRP comment same as for TDI:

- **State more clearly what adverse effects we are trying to prevent in a potentially exposed population**

MDI RELs

Sensitization and induction of MDI-asthma

Evidence that exposure at the REL should not result in sensitization:

1. **Acute, subacute and subchronic animal studies indicate the threshold for pulmonary irritation/inflammation and sensitization are interrelated, and fit C × t model**
2. **Reducing exposure reduces prevalence of occupational asthma**
3. **Toxicogenomic data suggest a large variation in response in human population (10-fold UF each for toxicokinetic and toxicodynamic differences); thus we used a 100-fold intraspecies UF**

MDI RELs

Can We Protect Sensitized Individuals?

- **What is the potential for exposure in individuals already sensitized?**
- **Will the RELs protect these individuals?**

1. **Rough estimate that only 12 – 43 individuals per million may be sensitized to any diisocyanate**
2. **Most chamber studies to confirm diisocyanate asthma start at 5 ppb and move up step-wise to 10 and 20 ppb, usually 30 min or less per exposure.**
   - **A few studies exposed sensitized individuals to 1 ppb MDI**
   - **Lowest reported was 0.5 µg/m^3 (0.05 ppb) for MDI**

MDI RELs

Can We Protect Sensitized Individuals?

Conclusion (Same as TDI):

- **RELs are lower than exposures used to detect diisocyanate asthma, and lower (8-hr/chronic RELs) than lowest reported concentration eliciting response**
- **RELs cannot be designed to protect all hypersensitive individuals (in our REL guidance)**
- **Likelihood that the risk of a sensitized individual being exposed to MDI emissions is very low**
- **The RELs are acceptable for the purposes of the Hot Spots program**

MDI
Other Changes to the Document

- **Added "List of Acronyms" at front of document**
- **Included more details on sampling and analysis techniques for both vapor and aerosol forms**
- **Added NIOSH non-occupational exposure study**
- **Added study summaries on thermal degradation of products made with MDI (with estimated MDI emissions)**
- **Added summaries of mechanistic studies that were recommended for inclusion**
- **Added summaries of DNA adduct studies**

MDI
Other Changes to the Document

- **Included more detail for studies summarized in the Toxicogenomics Section**
- **More clearly specified the type of diisocyanate workers were exposed to in the toxicogenomics studies**
- **Added Choi et al. (2009) TDI study to Toxicogenomics Section**

MDI
Other Changes to the Document

SRP Comment:

- **Explain high background level of pulmonary fibrosis in rats from the Hoymann et al. chronic study vs. the Reuzel et al. chronic study**

OEHHA Response: Included conclusions of two aging rat pulmonary pathology studies

1. **Aging rats can develop pulmonary fibrosis**
2. **Wistar rats from different colonies may show differences in fibrosis with age**

Response to Public Comments (presented to the SRP previously)

TDI Comments and Responses

We received comments on TDI from the

- **American Chemistry Council Diisocyanates Panel (ACC)**
- **Polyurethane Foam Association (PFA)**

TDI Comments and Responses

- **ACC and PFA Comment: Darcey et al. (2002) study investigating community complaints regarding emissions from a TDI facility has study limitations. OEHHA should also include Wilder et al. (2011) study that showed no community effects or emissions from TDI facilities.**

- **Response (pg. 3): OEHHA revised this section and included the Wilder et al. (2011) study: *"Possible exposure of the general population to TDI via emissions from a facility that used TDI to manufacture polyurethane foam has been reported (Darcey et al., 2002). However, a follow-up report at five TDI manufacturing facilities in the same state show one part per trillion to no current TDI exposures to nearby residents (Wilder et al., 2011)."***

TDI Comments and Responses

ACC and PFA Comment: OEHHA suggests free TDI may be emitted or extracted from foam products. OEHHA needs to include studies by Hugo et al. (2000), Vangronsveld et al. (2013) and CARB (1996) that show no exposures occur from polyurethane products.

Response (pg. 47): OEHHA has revised the section in question and included the suggested references. Revised sections note:

- ***… studies did not find emissions of detectable levels of free TDI from consumer products that were made with TDI …***
- ***… toluene-based extraction resulted in µg/g levels of free TDI extracted from the foam… The authors concluded that the TDI extracted from foam may have been due to decomposition of parts of the foam structure by the solvent, a process that is unlikely to occur under typical household uses.***

TDI Comments and Responses

ACC Comment: OEHHA incorrectly attributes accidental exposure of children to MDI when xylene was almost certainly the chemical children were exposed to. This is because of the 1) extreme volatility difference, 2) low MDI content (0.1% in xylene), and 3) is irrelevant because it does not reflect use of any TDI-based products.

Response (pg. 14): OEHHA revised the paragraphs in question and note: *"The authors (Jan et al., 2008) assumed all the symptomology was due to MDI even though xylenes also cause acute eye and respiratory symptoms. Thus, some proportion of the eye and respiratory effects could have been caused by xylene exposure."*

1) **Volatility difference may not matter; track was sprayed and solvent mixture was aerosolized**
2) **Low MDI content counterbalanced by high difference in toxicity (xylenes REL = 22 mg/m^3; TDI REL = 0.002 mg/m^3)**
3) **MDI has qualitatively similar effects to TDI and is relevant**

TDI Comments and Responses

ACC Comment: OEHHA inappropriately supports that the TDI released from foam explains (a) the wheezing by children using non-feather bedding (Strachan and Carey, 1995), (b) the higher incidence of asthma among firstborn children compared to their younger siblings (Karmus and Botezan, 2002)

Response (pg. 46): Text revised to note: 1) some studies found greater dust mite allergen in synthetic pillows and emphasized that no off-gassing of free TDI has been found, and 2) Karmus and Botezan study removed; no discussion of an association with new polyurethane products in study.

TDI Comments and Responses

ACC Comment: Childhood asthma is a Th2 driven process, while TDI-induced asthma is a Th1 driven process. Thus, if the Th2 pathway predominates in early life while the Th1 pathway is less well developed, children will be less sensitive – not more sensitive – to the development of diisocyanate asthma because it is primarily a Th1 driven pathway in humans.

Response (pg. 47): OEHHA revised and expanded the discussion of immune response in atopic asthma and TDI-induced asthma. Research shows both asthmatic states are more complex then simply saying one is Th1-driven and the other Th2-driven. Elements of both Th1 and Th2 pathways can be seen in both atopic asthma and TDI asthma.

TDI Comments and Responses

(Pgs. 47-48)

- **Also added that:** ***Regardless of the differences in T cell profiles, the clinical manifestations and pathophysiological changes observed in TDI-induced asthma are remarkably similar in some respects to those in atopic asthma including airway hyperreactivity, the presence of eosinophilic lung infiltrates (in some sensitized workers), and mucus hypersecretion in airways (Del Prete et al. 1993; Herrick et al., 2003).***

- **Finally, we state that:** ***"…differences in T cell profiles in childhood atopic asthma and diisocyanate-induced asthma does not inform us regarding the response of immune systems in infants and children to TDI exposure."*** **So, we can't assume children will be less sensitive to development of TDI-induced asthma.**

TDI Comments and Responses

ACC Comment: Use of the full default LOAEL to NOAEL UF of 10 for the acute REL based on 1/15 asthmatics responding to TDI exposure is too high. 1) The severity of this temporary effect is subjective and overly conservative, 2) the response frequency of 7% (1/15) at 10 ppb TDI is clearly approaching the NOAEL for this sensitive population, and 3) an UF of 3 provides a more objective yet still health-protective basis for a LOAEL to NOAEL UF.

Response (pgs. 8-10): 1) we consider an asthmatic response a severe adverse effect, 2) a second person responded to 20 ppb exposure, and 3) one-third of the group experienced sensory irritation and chest tightness during the exposures. Thus, we do not consider a 10-fold UF to be overly conservative.

TDI Comments and Responses

ACC Comment: A toxicodynamic UF of 3 ($\sqrt{10}$) is more appropriate to protect children with asthma because 1) asthma in children is primarily a Th2 driven process, and 2) most diisocyanate asthma is due to overexposure incidences well above 20 ppb.

Response (pgs. 60-61, 8-hr & chronic REL derivations):

- **It is inappropriate for OEHHA to assume that children will be less sensitive to the effects of TDI than adults. OEHHA views asthma as a disease that disproportionately impacts children. The potential to either induce or worsen asthma are considerations in assigning the value of the intraspecies UF.**
- **It is unclear how important high exposures are for inducing asthma. Some workers may be sensitized by long-term, low level exposures, others by mixed low-level and brief high exposures.**

TDI Comments and Responses

ACC Comment: OEHHA should explain specifically why it did not consider other studies (i.e., Ott et al. 2000), either alone or in combination with Diem et al., as the basis for its 8-hr and chronic RELs.

Response (pgs. 37-41): Ott et al. (2000) study was summarized in the text and in the table; Ott concluded that work exposures up to 5 ppb TWA found little correlation between TDI exposure and either FVC or FEV1 decrements.

- **Diem et al. established a NOAEL and LOAEL of 0.9 and 1.9 ppb, respectively for accelerated lung function decrement. It is a well-conducted study with an established NOAEL and LOAEL lower than the Ott et al. study conclusion.**

TDI Comments and Responses

ACC Comment: Longer-term studies (Ott et al., 2000) indicate that a subchronic UF = 3 (√10) is not justified. No lung function decrements found in Ott et al. study (mean exposure 9.3 years), and the longer the duration of TDI exposure the lower the risk of developing TDI-induced asthma.

Response (pgs. 37-41): Ott et al. conclusion was at 5 ppb or less, no lung function decrements observed (a free-standing NOAEL), sensitization incidence was 0.7% per year.

- **Diem study found a NOAEL and LOAEL below 5 ppb for lung function decrements in 5 year study - default subchronic UF used because study duration <12% of human lifespan. Incidence/severity of this lesion may increase with exposures longer than 5 yrs.**
- **Mean latency to sensitization - 7.3 years (Malo et al. 1992) subchronic UF also to protect individuals who become sensitized with lower-level exposure over a longer period of time.**

TDI Comments and Responses

ACC Comment: OEHHA inappropriately uses a time-adjusted exposure for the 8-hour REL based on the chronic REL using the supposition that TDI may cause respiratory sensitization with only intermittent low-level exposures.

Response (pg. 60): OEHHA has revised the time-adjusted exposure for the 8-hour REL from 0.001 ppb to 0.002 ppb due to a duration-dependent component for pulmonary effects:

- **Acute C × t studies in rodents – duration & conc. equally important**
- **Some recovery occurs with 6-hour daily exposures vs. 18-hour daily exposures in MDI rodent studies**
- **C × t studies in TDI-sensitized subjects observed that bronchial responsiveness was neither exclusively concentration- nor duration-dependent**

TDI Comments and Responses

ACC Comment: $10m^3$ / $20m^3$ adjustment factor not needed for extrapolation for the chronic REL. Acute studies in rodents show no sensory irritation or inflammation below 23 ppb [suggesting threshold].

Response (pg. 61):

- **Unclear in humans that pulmonary function changes based on 8 hr worker exposures will also be protective for continuous chronic exposure, so we use the standard default $10m^3$ / $20m^3$ adjustment.**
- **Acute studies may not be particularly relevant for chronic exposures.**

TDI Comments and Responses

ACC Comment: a 10-fold intraspecies toxicokinetic (TK) UF for the 8-hour and chronic RELs is inappropriate. Diem et al. study already includes potentially sensitive workers, so no TK UF needed.

Response (pg. 62): An intraspecies TK UF = 10 was applied:

- **to account for the up to 10-fold greater susceptibility (based on mean OR values) to diisocyanate induced asthma in workers with specific gene variants associated with metabolizing enzymes including GSTM1, GSTP1, EPHX, and NAT1.**
- **General population likely more genetically varied than worker population.**

TDI Comments and Responses

ACC Comment: An intraspecies toxicodynamic (TD) UF of 10 is not supported by scientific evidence indicating children are less sensitive to TDI-induced lung function decrements: children are less sensitive because TDI asthma is primarily a Th1 driven process

Response (pg. 62): We applied an intraspecies TD UF = 10 to account for:

- **pharmacodynamic variability among humans, including infants and children.**
- **Increased odds of developing isocyanate-induced asthma was associated with a number of genes related to toxicodynamic variability, including genes involved in immune regulation, inflammatory regulation, and antioxidant defense.**
- **No evidence that children are less sensitive to TDI-induced sensitization and pulmonary lung function decrements.**

MDI Comments and Responses

We received comments on MDI from the

- **American Chemistry Council Diisocyanates Panel (ACC)**

MDI Comments and Responses

Comment: Genotypic variation in MDI metabolic enzymes is not a relevant consideration for development of RELs for MDI.

- **The formation of glutathione adduct with MDI is not enzyme mediated, genetic polymorphism is not expected to affect adduct formation.**

Response (pgs. 34-37): Researchers point out that MDI can react directly with GSH, and that GSTs can help facilitate the reaction of GSH with MDI. GSTs are critical in the protection of cells from reactive oxygen species, which are generated by diisocyanates.

The genomic data indicate that variation in GST enzyme activities are modifiers of susceptibility of diisocyanate-induced asthma.

MDI Comments and Responses

Comment: The information on associations between genes and isocyanate-induced risk is limited and not consistent, and there are contradicting reports in the literature for the importance of N-acetyltransferase reactions.

Response: Several researchers have observed that genetic variants of antioxidant defense genes for GSTs and NATs are associated with increased susceptibility to diisocyanate-induced asthma. However, there are some contradictions in the literature. We added language noting this.

MDI Comments and Responses

Comment: MDI causes portal of entry effects and available data have been unable to show that metabolism contributes in any significant way to the immune response effects caused by MDI.

Response (pg. 5): A number of researchers believe diisocyanates may react with proteins, possibly via GSH conjugates, to form protein conjugates. The protein conjugates may be immunogenic, and the formation of hapten complexes may give rise to immunological reactions. Work by Wisnewski et al. indicates that GSH can act as a "shuttle" for MDI. Once MDI-GSH is absorbed, MDI-albumin conjugates are generated via GSH-mediated transcarbamoylation, which exhibit distinct changes in conformation and charge. These MDI-albumin conjugates are specifically recognized by serum IgG of MDI workers with diisocyanate-induced asthma, suggesting one possible pathway for MDI in promoting immune responses.

MDI Comments and Responses

Comment: Even the highest levels of respirable MDI aerosol (found in workplaces where spraying applications were conducted) are a factor of 2400 below the 4-hour acute LC50 in animals.

Response: The adverse effects the RELs are based on are respiratory irritation/inflammation and/or lesions to respiratory tissue, not LC50s. Our proposed RELs range from 0.08 to 6 µg/m^3, which is well within levels generated during workplace operations.

MDI Comments and Responses

Comment: Researchers have shown that after removal from further exposure, the majority of individuals with diisocyanate related asthma show improvement or totally recover.

Response (pgs. 15-16): At the suggestion of the commenter, we added more language than we had in the document about the potential for recovery following sensitization to diisocyanates.

MDI Comments and Responses

Comment: OEHHA failed to review the recent publication on neurotoxicity (Hughes *et al*. 2014) which reviews the Reidy and Bolter study and points out numerous limitations in this paper for links between neurological effects and MDI exposure.

Response (pgs. 22-23): We had already noted in the MDI REL document that there are limitations in the Reidy and Bolter study. We included a summary of findings by Hughes et al. (2014) in the REL document, pointing out additional limitations in the Reidy and Bolter study.

MDI Comments and Responses

Comment: For the acute, 8-hr and chronic RELs, the use of 3 or 10-fold interspecies toxico[kinetic] (TD) UFs for metabolic variability is inappropriate because MDI is a direct acting irritant on lung tissue.

Response (pg. 41): A default interspecies toxicokinetic (TK) UF is applied when there is little or no data on TK interspecies differences, whether or not the chemical is a direct or indirectly acting agent on respiratory epithelial tissue. This is consistent with our default uncertainty factor approach used in deriving RELs.

MDI Comments and Responses

Comment: For the acute, 8-hr and chronic RELs, an intraspecies toxicodynamic (TD) UF of 10 is not appropriate because genotypic variations in metabolic enzymes are not relevant to MDI, and because children should be less sensitive – not more sensitive – to the sensitizing effects of diisocyanates (i.e., childhood asthma is Th2-driven, as opposed to diisocyanate sensitization which is Th1-driven)

Response (pgs. 34-37): A number of gene variants (e.g., GST enzymes) have been reported to be associated with increased sensitivity to the disease in workers, which suggests that diisocyanate-induced asthma represents a complex disease phenotype determined by multiple genes. Mean OR values were up to 10.

Also, It is unknown how children will react to MDI exposure early in life when the immune system is still developing.

MDI Comments and Responses

Response continued: Further, OEHHA considers asthma to be a disease that disproportionately impacts children. Thus, whether MDI induces asthma or triggers existing asthma in children, we would use a higher toxicodynamic uncertainty factor to protect children, as we have for other RELs.

MDI Comments and Responses

Comment: The 8-hr REL was derived by OEHHA using a time-adjusted exposure concentration (20 m^3/10 m^3) calculated in a manner inconsistent with OEHHA guidance and practice. OEHHA is mixing rodent and human exposure approaches in a less than transparent manner to reduce the standard time-adjustment factor.

Response: Our Noncancer Guidelines (OEHHA, 2008) show that it is appropriate to use the 20m^3/10m^3 conversion for 8-hour RELs based on a chronic exposure study. For example, we have used this conversion for acrolein and acetaldehyde 8-hour RELs that are based on rat studies with exposures of 6 hours/day, 5 days/week. As noted in our acetaldehyde REL, *"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."*

MDI Comments and Responses

Comments: For the 8-hr and chronic RELs, OEHHA should transparently indicate that its selection of a 5% benchmark response (BMR) is a policy decision that results in a 3-fold lower BMCL than was calculated by USEPA which used a 10% BMR to derive a REL-like value (RfC) for MDI from the same dataset.

Response: OEHHA presents our use of the 5% benchmark response (BMR) in our Noncancer Guidelines (OEHHA, 2008) and cites supporting documentation showing why the 5% BMR appears to be equivalent to a NOAEL in well designed and conducted animal studies. A response range of 1% to 5% approximates the lower limit of adverse effect detection likely to occur in typical human epidemiological studies, and in large laboratory animal studies the detectable response rate is typically in the 5 to 10% range (Gaylor, 1992).

Next Steps