

Responses to Public Comment on the Draft Reference Exposure Levels for Toluene Diisocyanate

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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On July 4, 2014, the Office of Environmental Health Hazard Assessment (OEHHA) released the draft document, [Toluene Diisocyanate Reference Exposure Levels: Technical Support Document for the Derivation of Noncancer Reference Exposure Levels](#) to solicit public comment. Responses to comments received on the draft toluene diisocyanate 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 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 revise the existing chronic REL of 0.07 $\mu\text{g}/\text{m}^3$ for toluene diisocyanate, and derive new acute and 8-hour RELs.

Commenters on the Draft RELs for toluene diisocyanate (TDI)

Comments were received from:

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

Responses to Comments Received from ACC

ACC Comment 1:

“**Overview:** Although the 2014 TDI REL document (73 pages) prepared by OEHHA has expanded on the 2010 version (19 pages), the document’s conservative bias, as demonstrated by its proclivity for an unbalanced presentation of available data and uncritical data analyses, remains largely intact. The two key studies identified by OEHHA for the acute REL and 8h / chronic REL are reasonable but the scientific rationale justifying the selection of some uncertainty factors (UFs) is weak. Specific issues are outlined below and supplemented with earlier ACC comments, as appropriate.”

Response to ACC Comment 1:

The rationale for the selection of uncertainty factors for the RELs is based on guidance in our Noncancer Technical Support Document (OEHHA, 2008). Further details concerning decisions for selecting uncertainty factors are discussed in the responses to comments below.

Reference:

OEHHA. (2008). *Air Toxics Hot Spots Program Risk Assessment Guidelines. Technical Support Document for the Derivation of Noncancer Reference Exposure Levels* California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Oakland, CA. Online at:
http://www.oehha.ca.gov/air/hot_spots/rels_dec2008.html.

ACC Comment 2:

“**OEHHA (Section 3, pg 3) states ‘The general population may be exposed to TDI via emissions from facilities that use TDI and use of consumer products containing this compound (Darcey et al., 2002; Krone and Klingner, 2005).’ This is an example of unbalanced study selection.**

OEHHA suggests that the general population may be exposed to emissions from TDI facilities based on complaints of headache, nausea and respiratory symptoms (irritation, shortness of breath) from 38 residents near a polyurethane foam facility suspected of releasing TDI and methylene chloride (Darcey et al., 2002). Although six residents were reported to have antibodies to one or more of three diisocyanates (TDI, MDI, HDI), diisocyanate antibodies were not found in any of the eight residents clinically diagnosed with hyperactive airway disease. Despite the study limitations (e.g., lack of a definitive diagnosis of TDI respiratory sensitization, lack of control community population, and potential cross-reactivity among diisocyanates) as well as criticism of the analytical and

exposure assessment methodologies employed (Levine *et al.*, 2001), the study did precipitate a broader and more thorough investigation by National and North Carolina State health organizations of communities in close proximity to TDI emission sites (Wilder *et al.*, 2011). Focusing on the facilities with the highest TDI emissions (based on 7-year average TRI releases reported to the State), the authors concluded there was no significant difference between the targeted and comparison communities in the prevalence of either asthma or asthma-like respiratory symptoms and that air sample and antibody test results were not consistent with recent or ongoing exposures to TDI.

Response to ACC Comment 2:

The comment by ACC refers to the brief account in Section 3 of a study that suggests there was potential neighborhood exposure to facility TDI emissions:

“The general population may be exposed to TDI via emissions from facilities that use TDI and use of consumer products containing this compound (Darcey et al., 2002; Krone and Klingner, 2005).”

OEHHA intended to show that there are some uncertainties about the Darcey et al. study by using the phrase, “*may be exposed to TDI via emissions from facilities...*” OEHHA will include a brief summary of the Wilder et al. (2011) study and revise the paragraph to read as follows, “*Occupational exposure to TDI may occur through inhalation and dermal contact during its production or use. 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).*”

ACC Comment 3:

“OEHHA also suggests unreacted TDI may be released from foam products based on a publication by Krone and Klinger (2005) who developed a methodology (Krone *et al.*, 2003) that purportedly extracts free isocyanate from foam under a physiological (milling, solvent) conditions. Their publication speculates that this extractable isocyanate can be released from foam under physiological exposure and may explain, at least in part, asthma seen in children. OEHHA includes some of this speculation elsewhere within its REL document (Section 6.2). However, it is unclear why OEHHA did not consider an earlier study (Hugo *et al.*, 2000) showing that under more relevant conditions free isocyanate is not emitted from foam (detection limit ~ 0.1 ppb (v/v) in air) even when the foam is purposely loaded with free TDI to ~ 1 ppm (w/w). The Diisocyanates Panel (Panel) notes that the observations by Hugo *et al.* (2000) were recently supplemented by two studies conducted by the International Isocyanate Institute (III) on the emission (to air) and migration (to contact medium) of TDI from foam (Vangronsveld *et al.*, 2013a; Vangronsveld *et al.*, 2013b). The release of free TDI could not be detected in either

media. This conclusion is consistent with that of the California EPA (1996) which was unable to detect TDI from residential foam products even when subjected to elevated temperature and loading conditions. In addition, the III studies showed that, with solvent based extractions of PU foams (such as those conducted by Krone *et al.*), a significant portion of the extractable TDI is likely due to degradation of trace impurities in the foam by the solvent.

Response to ACC Comment 3:

OEHHA has revised the first and second paragraphs of Section 6.2 to include the findings of Hugo *et al.* (2000), Vangronsveld *et al.* (2013) and CARB (1996) taking into consideration that detectable levels of air emissions have not been found from products made with TDI (this was already noted previously by OEHHA), and that solvent extraction techniques used to assess release of free diisocyanates may actually cause decomposition of the test material to form free TDI. The beginning of the first paragraph now reads as follows:

*“No studies of inhalation exposures to TDI among children were located. It has been postulated that early life exposure to TDI may occur through inhalation and dermal contact with polyurethane products (Krone *et al.*, 2003).”*

The second paragraph then presents the air emission and extraction results:

*“In addition, two studies did not find emissions of detectable levels of free TDI from consumer products that were made with TDI (e.g., carpet padding, mattress and furniture foam, varnishes and sealants) (Hugo *et al.*, 2000; CARB, 1996). Krone *et al.* (2003) applied semiquantitative tests (i.e., wipe test and extraction with dimethyl sulfoxide) for isocyanate to polyurethane products, including mattresses, mattress pads, sofa padding, carpet pads and pillows, and detected free isocyanate in these consumer products. It was suggested that isocyanate may be available to dissolve in skin oils upon dermal contact. A similar study by Vangronsveld *et al.* (2013) used various solvent systems and detection methods to extract free TDI from flexible polyurethane foam. A toluene-based extraction technique was deemed the most consistent and resulted in $\mu\text{g/g}$ 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.”*

ACC Comment 4:

OEHHA (Section 4, pg 4) states that according to Timchalk *et al.* (1994) “... essentially all the TDI is retained ...” after an inhalation exposure, incorrectly implying that inhaled TDI is not eliminated from the body. Timchalk *et al.* (1994) conclude that essentially all of the inhaled TDI is initially retained in the lungs but is then

subsequently excreted primarily in feces, likely as polyurea. Although, as one might expect, fecal excretion of TDI after an inhalation exposure is slower than that seen after an oral exposure, 48 h post-exposure the majority of the inhaled dose is recovered in the feces / intestinal contents (64%), a value comparable to that seen after an oral (gavage) exposure (83%). The excretion pattern is essentially identical to that described by Gledhill *et al.* (2005) for MDI.

Response to ACC Comment 4:

The phrase "...essentially all the TDI is retained..." is the wording choice used by Timchalk *et al.* (1994). . This suggests that essentially all the TDI is absorbed when inhaled, and none exhaled. This would refer to essentially 100% retention of the inhaled TDI, or 100% inhalation absorption. We will revise the sentence and remove the word "retained" to avoid any misunderstanding:

*"In experimental administration by the oral route, 12-20% of the dose was absorbed, while by the inhalation route, essentially all the TDI was absorbed (Timchalk *et al.*, 1994). At 48 hours post-inhalation exposure, approximately 15 and 47% of the recovered metabolites was in urine and feces, respectively."*

ACC Comment 5:

OEHHA (Section 5.2, pg 14) uses the Jan *et al.* (2008) article on the purported exposure of school children to MDI to suggest that children may be similarly exposed to TDI. This speculation is inappropriate on several levels and is irrelevant to TDI-based products. First, although OEHHA acknowledges (pg 45) that "no studies of inhalation exposures to TDI among children were located," it goes on to describe exhaustively asthma-like symptoms reported by school children purportedly exposed to MDI (Jan *et al.*, 2008). However, a more critical evaluation of the limited data provided indicates that the reported symptoms are Reactive Airways Dysfunction Syndrome (RADS)-like symptoms (e.g., cough, wheeze, headache) almost certainly due to xylene, a known CNS (central nervous system) depressant and upper respiratory tract irritant that was used as a solvent for the applied MDI. In addition, the Panel notes that (a) no air monitoring was conducted for either volatile organic compounds or MDI, and (b) despite the claim by Jan *et al.*, an earlier work cited by the authors did not detect MDI near polyurethane tracks up to a week after application. Examination of the Jan *et al.* referenced work (Chang *et al.*, 1999) reveals no mention of MDI measurements. Further support for the absence of an exposure to MDI comes from the observation that no MDA (methylene dianiline) was detected in the hydrolyzed urine of school children purportedly exposed to MDI. However, the following factors actually indicate that the symptoms observed were most likely due to the inhalation of xylene: the extreme (> 1 million-fold) difference in volatility between xylene and MDI, the high xylene content compared to MDI in the applied product (0.1% MDI in xylene), as well as

the symptoms consistent with xylene or other solvent exposure. Second, the exposure scenario described in the Jan *et al.* (2008) article (i.e., application of a solvent-based athletic track material) does not reflect the use of any TDI-based product and is therefore irrelevant to the estimation of TDI exposure potential.

OEHHA should remove this reference as an example of TDI “toxicity to infants and children” and as a basis for childhood exposure and sensitivity to diisocyanates since (a) the health effects seen can be attributed solely to the highly volatile solvent, xylene and (b) the exposure scenario described in the article is not a relevant TDI application.

Response to ACC Comment 5:

Due to the structural and toxicological similarities of the two compounds (both are aromatic ring diisocyanates) OEHHA believes it is reasonable to use the MDI exposure incident in children if there is no other example for TDI exposure in children in the literature.

Regarding part (a) of ACC’s comment, OEHHA also noted in the REL summary that air monitoring was not conducted for MDI (or xylene). However, the authors report that they conducted a simulated spraying operation of the mixture and measured MDI levels of 870 ppm w/w in xylene. Considering ppb levels can cause respiratory effects, it seems plausible that a spraying/paving operation could result in significant MDI exposure, as well as significant xylene exposure, to children in school classrooms less than 100-240 meters downwind of the operation. To clarify this matter, OEHHA has added more details about the exposure and added information about the simulated spraying results to Section 5.2.

Regarding part (b) of ACC’s comment, OEHHA reviewed the Chang *et al.* (1999) study. This study does not appear relevant to the results of Jan *et al.* (2008) because Chang *et al.* were measuring VOC off-gassing from tracks after they were installed, not during application of the tracks. In addition, Chang *et al.* did not measure any emissions from a track installation operation that consisted of MDI mixed in xylenes. Further, it is unclear if Chang *et al.* even attempted to measure emissions of isocyanates from track surfaces. OEHHA agrees with ACC that the assertion by Jan *et al.* that, “*Adjacent to such tracks, air levels of MDI were easily detectable even after the first week of track installation*” was not at all discussed in Chang *et al.* as reported in their study. One possibility for this discrepancy is that Jan *et al.* may have included the wrong reference in their reference section.

The comment by ACC that, “*...no MDA was detected in the hydrolyzed urine of school children purportedly exposed to MDI*” was noted by the authors. However, the authors attributed this finding to the short exposure time of the children. Urine sample collection was also delayed until three days following the exposure incident. OEHHA has added the following sentence to address this finding:

“A spot urine test did not reveal a positive reaction for MDA in acid-hydrolyzed urine samples. The authors attributed this finding as characteristic of a brief exposure to MDI.”

The final comment by ACC is that the extreme difference in volatility between xylene and MDI would support xylene as the major cause of the respiratory symptoms in the children. OEHHA notes that the extreme difference in volatility is somewhat balanced out by the extreme difference in toxicity between the two chemicals. The OEHHA acute REL for xylenes is 22,000 $\mu\text{g}/\text{m}^3$ whereas the proposed acute REL for MDI is 6 $\mu\text{g}/\text{m}^3$ (0.6 ppb). The vapor pressure for xylenes is about 8 mm Hg at 25°C whereas the vapor pressure for MDI is 5×10^{-6} mm Hg @ 25°C. Jan et al. described the track application process briefly as a spraying operation. Thus, the volatility issue raised in the comment may be of little consequence because both xylene and MDI would be essentially aerosolized upon release and may have reached the school rooms in roughly equal proportions as found in the original emission source.

Finally, the critical effects of the acute REL for xylenes are nervous system, eye irritation and respiratory irritation. The reports of dizziness by the children could be due to exposure to xylenes. However, no evidence could be found in the literature that acute exposure to xylenes causes RADS-like effects as ACC suggests. OEHHA will add the following sentences, *“The authors 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.”*

ACC Comment 6:

After acknowledging that no examples of either TDI inhalation exposures among children or detectable levels of TDI from bedding materials could be located, and ignoring the published data demonstrating that isocyanates are not released from such polyurethane products (Cal EPA, 1996; Hugo *et al.*, 2000; Vangronsveld *et al.*, 2013a and 2013b), OEHHA (Section 6.2, pg 45) uses the solvent-based wipe test by Krone *et al.* (2003) – addressed under 1a above - to support its contention that free isocyanate is present in consumer bedding. OEHHA then further uses this isolated, cherry-picked observation inappropriately to support its hypothetical claims 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), and (c) the greater sensitivity of infants/young children to TDI-induced asthma. As indicated below, these three claims are inappropriate.

Regarding the first claim, the Panel notes that diisocyanate measurements were not made in either study and that the emission of TDI from foam products could not be

detected in studies designed to do so (Cal EPA, 1996; Hugo *et al.*, 2000). OEHHA should acknowledge that wheeze associated with non-feather bedding likely reflects the fact that synthetic pillows harbor significantly more dust mites, a major factor for childhood asthma (Peat *et al.*, 1996), than feather pillows (Crane *et al.*, 1997).

Response to ACC Comment 6:

OEHHA has revised this part of Section 6.2 to include briefly the findings by California Air Resources Board (1996), Hugo *et al.* (2000), Vangronsveld *et al.* (2013), Strachan and Carey, (1995) and Crane *et al.* (1997). The first paragraph under Section 6.2 now reads:

*“No studies of inhalation exposures to TDI among children were located and it is unknown how early-in-life exposures to TDI would affect the immature immune system. It has been postulated that early life exposure to TDI may occur through inhalation and dermal contact with polyurethane products (Krone *et al.*, 2003). Strachan and Carey (1995) found independent associations between severe wheeze and the use of non-feather bedding, especially foam pillows (odds ratio 2.78; 95% C.I. 1.89 to 4.17), among children with 12 or more wheezing attacks in the previous 12 months,. The authors speculated that volatile organic compounds could be off-gassing from the foam pillows. However, other researchers found that there is increased exposure to house dust mite allergen from synthetic pillows compared to feather pillows and that this may explain the increased asthma symptoms (Crane *et al.*, 1997).*

The second paragraph of Section 6.2 includes findings of the California Air Resources Board (1996), Hugo *et al.* (2000) and Vangronsveld *et al.* (2013) and is addressed in Response to ACC Comment #3 above. Regarding the comment about the Karmus and Botezan (2002) study, see Response to Comment #7 below.

ACC Comment 7:

Regarding the second claim, OEHHA should also acknowledge the speculative nature of its association between asthma in firstborn children and exposure to new polyurethane products based on Karmaus and Botezan (2002). This article reviewed multiple publications addressing the question of whether or not subsequent siblings were afforded protection from various manifestations of allergy and asthma. The authors noted that this sibling effect “is more consistent for hay fever and sensitization than for asthma or wheezing and eczema.” The authors examined several possible explanations for the sibling effect and concluded that “no comprehensive biological explanation has yet emerged.” The authors never offered exposure to polyurethane products as a potential explanation; this speculation originated with OEHHA, apparently based on the observation by Krone and coworkers (2003) that their solvent-based technique showed a “general trend toward lower concentration in older samples.” There was no indication that this “trend” was statistically significant; indeed the qualitative

information provided by Krone and coworkers showed little, if any, differences among sample foams aged 6 months to 30 years. OEHHA's "high exposure from new foam pillows" hypothesis also runs counter to the air extraction study by Hugo *et al.* (2000) that found no TDI emitted from two-week old foam, purposely selected as the "freshest" foam that could reach the market in mattresses. Furthermore, OEHHA's contention runs counter to EPA's statement in the TDI Chemical Action Plan, stating that "polyurethane products, such as mattresses, pillows, and bowling balls, are considered completely cured products before they are sold. Completely cured products are fully reacted and therefore are considered to be inert and non-toxic." (EPA, 2011)

Response to ACC Comment 7:

The study by Karmus and Botezan (2002) was removed from the REL summary (see above). The primary focus and finding of this study was decreased allergy and asthma among families with more children, compared to families with fewer children. It briefly discussed higher incidence of asthma among firstborns, but the article itself did not include any discussion of an association with new polyurethane products. Because of this lack of association we decided to remove the summary from the REL document.

ACC Comment 8:

Regarding the third claim, OEHHA combines speculative childhood exposures to TDI in foam (above) with the observation (Prescott *et al.*, 1999) that "at birth, humans exhibit a dominant humoral (Th2) responsiveness (i.e., atopic state)" to support its claim that young children are at greater risk for the development of TDI-induced asthma because it is a Th2 driven process. However, TDI-induced asthma is not Th2 driven. It is clear that the pathophysiologies 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 TDI asthma lack an association with atopy and exhibit a very low prevalence of IgE antibodies as well as a very high prevalence of CD8+ T (Th1) cells obtained via lung biopsy (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 TDI-induced asthma is primarily a Th1 driven pathway.

Response to ACC Comment 8:

OEHHA is revising the paragraph in question (3rd paragraph under Section 6.2 in the REL summary) because a discussion of immune factors generated from TDI-induced sensitization is more complex than currently presented.

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

TDI-induced asthma studies in adult humans and animal models have shown a selective Th2 type or a mixed Th1/Th2 immune response (Johnson et al., 2007; Kimber et al., 2007; Lummus et al., 1998; Maestrelli et al., 1997). Skin sensitizing chemicals usually induce preferential Th1-type responses. Thus, stating that TDI-induced asthma is primarily a Th1 driven pathway represents something of an oversimplification. TDI appears 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, TDI-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 TDI, 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.

Finally, this discussion does not directly address the critical effects used for the 8-hour and chronic derivation of the REL (i.e., accelerated decline in long-term lung function as measured by FEV₁). As discussed in the REL summary, a REL could not be developed based on sensitization because there is currently no consensus on the threshold-sensitizing inhalation dose for TDI. However, as discussed in Section 8.3, we believe the REL based on accelerated decrease in FEV₁ should protect most individuals from diisocyanate-induced sensitization.

The new paragraphs discussing the TDI immune response now reads:

“It is unknown how the immune system in infants and children would respond to TDI exposure during critical stages of immune system and respiratory system development. At birth, humans exhibit a dominant humoral, T_H2 , responsiveness (i.e., an atopic state). During the first few years of life, the T_H2 response converts to a more cellular (T_H1) immune response characteristic of the mature adult immune system. A delay in the transition from the predominant T_H2 pattern to the more balanced T_H1/ T_H2 response allows an atopic T_H2 type response to persist longer, thus extending the period of vulnerability to environmental stressors and allergens, and increasing the likelihood of subsequent disease expression including asthma (Prescott et al., 1999; Wills-Karp, 1999). Contrary to a T_H2 pattern for childhood atopic asthma, obese children with asthma exhibit T_H1 polarization and greater asthma severity, whereas lean children with asthma exhibit T_H2 polarization and less asthma severity (Youssef et al., 2013). The presence of high leptin levels in the obese children is associated with an increase in IFN- γ production by T_H1 -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 T_H1 - or T_H2 -driven pathways can be involved in childhood asthma.

While there is evidence that atopic asthma in children is usually T_H2 -based, the immunopathogenesis of diisocyanate-induced asthma is less distinct. TDI-induced asthma in workers has shown either a T_H1 immune response pattern (Maestrelli et al., 1994; Finotto et al., 1991) or a mixed T_H1/ T_H2 immune response (Maestrelli et al., 1997; Redlich et al., 1997; Lummus et al., 1998). 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 (but only in some sensitized workers), and mucus hypersecretion in airways (Del Prete et al. 1993; Herrick et al., 2003).

Similar to development of childhood allergic asthma, TDI-induced asthma is multifactorial in origin and complex. The mechanism of sensitization by TDI is not well understood in adults, much less children. Thus, 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.”

References:

Ban, M., et al. (2006). TDI can induce respiratory allergy with Th2-dominated response in mice. Toxicology **218**(1): 39-47.

Del Prete GF, De Carli M, D'Elis MM, Maestrelli P, Ricci M, Fabbri L and Romagnani S (1993). Allergen exposure induces the activation of allergen-specific Th2 cells in the airway mucosa of patients with allergic respiratory disorders. Eur J Immunol **23**(7): 1445-9.

Finotto S, Fabbri LM, Rado V, Mapp CE and Maestrelli P (1991). Increase in numbers of CD8 positive lymphocytes and eosinophils in peripheral blood of subjects with late asthmatic reactions induced by toluene diisocyanate. *Br J Ind Med* 48(2): 116-21.

Herrick CA, Das J, Xu L, Wisnewski AV, Redlich CA and Bottomly K (2003). Differential roles for CD4 and CD8 T cells after diisocyanate sensitization: genetic control of TH2-induced lung inflammation. *J Allergy Clin Immunol* 111(5): 1087-94.

Johnson VJ, Yucesoy B, Reynolds JS, Fluharty K, Wang W, Richardson D, Luster ML. 2007. Inhalation of toluene diisocyanate vapor induces allergic rhinitis in mice. *J Immunol* 179:1864-1871.

Kimber et al. 2007. Chemical respiratory allergy: Opportunities for hazard identification and characterization. *ATLA* 35:243-265.

Lummus ZL, Alam R, Bernstein JA and Bernstein DI (1998). Diisocyanate antigen-enhanced production of monocyte chemoattractant protein-1, IL-8, and tumor necrosis factor-alpha by peripheral mononuclear cells of workers with occupational asthma. *J Allergy Clin Immunol* 102(2): 265-74.

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Prescott SL, Macaubas C, Smallacombe T, Holt BJ, Sly PD and Holt PG (1999). Development of allergen-specific T-cell memory in atopic and normal children. *Lancet* 353(9148): 196-200.

Redlich CA, Karol MH, Graham C, Homer RJ, Holm CT, Wirth JA and Cullen MR (1997). Airway isocyanate-adducts in asthma induced by exposure to hexamethylene diisocyanate. *Scand J Work Environ Health* 23(3): 227-31.

Wei B, Zhang H, Li L, Shang Y. 2011. T helper 17 cells and regulatory T-cell imbalance in paediatric patients with asthma. *J Int Med Res* 39:1293-1305.

Youssef DM, Elbehidy RM, Shokry DM, Elbehidy EM. (2013). The influence of leptin on TH1/Th2 balance in obese children with asthma. *J Bras Pneumol* 39(5):562-68.

Wills-Karp M (1999). Immunologic basis of antigen-induced airway hyperresponsiveness. *Annu Rev Immunol* 17: 255-81.

ACC Comment 9:

OEHHA supports its claim that TDI-induced asthma is primarily a Th2 driven process with two studies in mouse models of TDI-induced asthma. Beyond the fact that there are no generally accepted animal models for TDI-induced asthma in humans and that results in juvenile mice may not be reliable predictors for effects in infants, there are several concerns with these studies.

The first study on this topic (Matheson *et al.*, 2005b) evaluated the effects of TDI inhalation exposures in control and CD4 (Th2) and CD8 (Th1) knockout (KO) mice. Although the authors claim their results support TDI-induced asthma being a primarily Th2 driven process, a balanced examination of the data provides a different picture. All meaningful measures of the atopic state (e.g., airway hyperreactivity to methacholine challenge, IgE production, airway remodeling, presence of eosinophiles and eosinophile peroxidase activity in bronchial alveolar lavage fluid, mRNA expression of Th2 cytokines) were equally affected (diminished) in Th2 and Th1 KO mice compared to wild-type mice. The Matheson *et al.* (2005b) data in mice indicate that Th1 pathway cytokines (e.g., interferon γ) participate in the full manifestation of the asthmatic response just as they do in children (e.g., bronchial hyperreactivity) exposed to environmental allergens (Heaton *et al.*, 2005) as well as adults exposed to TDI (Liu and Wisnewski, 2003). Thus, while the Th2 pathway (enhances atopy) / Th1 pathway (antagonizes atopy) paradigm described by OEHHA in support of the TDI REL may apply to other asthmogens, it is clear that diisocyanates, as low molecular weight asthmogens, do not fit the standard paradigm. As a consequence, 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 to ACC Comment 9:

The summary of the Matheson *et al.* study was removed from this section because its relevance for childhood exposure to TDI is not apparent (i.e., only adult mice were exposed in the study). The main feature of this section should be exposures during childhood development.

The statement that “children will be less sensitive – not more sensitive – to the development of diisocyanate asthma 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 TDI 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 TDI-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. Further, as described in 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 due 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 factor.

Regarding specific criticisms of the animal study summarized, Matheson et al. (2005b) concluded in their mouse model study that, "*These studies indicate that occupational asthma, induced by low molecular-weight chemicals, represented in these studies by TDI, evokes similar immune mechanisms as allergic asthma caused by large-molecular-weight antigens. Activated CD41 T cells play a predominant role in the pathogenesis of TDI-induced asthma. Furthermore, it would appear that Th2 cytokines are decisive in the initial phase of occupational asthma, in the priming and development of Th2 cells, and in the permeation of eosinophils into the airway lumen.*" The authors go on to acknowledge that, "*a cooperative interaction with CD81T cells and Th1 cytokines in the pathogenesis of asthma lesions clearly exists. This was particularly evident with IFN γ and the development of AHR and the reduction of AHR, inflammation, and Th1/Th2 cytokine production in CD8 knockout mice.*"

Thus, the authors seem to acknowledge that their animal model exhibits a mixed T cell response, not unlike what can be seen for TDI-induced asthma in humans (*Maestrelli et al., 1997; Redlich et al., 1997; Lummus et al., 1998*).

Reference

OEHHA (2001). *Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act*. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Oakland, CA. Online at: http://oehha.ca.gov/air/toxic_contaminants/SB25finalreport.html.

ACC Comment 10:

The second study (Ban *et al.*, 2006) noted that mice sensitized to and subsequently challenged with TDI by inhalation exhibited a predominant Th1 type response, while mice sensitized by both topical application and intratracheal installation of TDI resulted in a predominant Th2 type response when subsequently challenged with TDI by intratracheal installation. There are several flaws with using this study to support a higher sensitivity of children to TDI-induced asthma. First, as discussed above, multiple studies have shown that TDI is not released from fully cured consumer products (e.g., polyurethane foam) made with TDI, even foam purposefully loaded with TDI. Thus, notwithstanding the isolated solvent based wipe test protocol developed by Krone *et al.*

(2003), dermal exposures to TDI in fully cured consumer products are simply not a realistic scenario. Second, OEHHA does not substantiate the relevance of the artificial sensitization protocol (dermal application followed by intratracheal administration of TDI in olive oil) required to generate a Th2-type response in mice to hypothetical childhood exposures to TDI. The Panel notes that the slightly more physiological (albeit still unrealistic) sensitization protocol used by Ban *et al.* (2006) in mice (i.e., subcutaneous administration of TDI followed by inhalation to TDI) failed to result in a Th2-type response comparable to that seen with their topical / intratracheal sensitization protocol.

Response to ACC Comment 10:

OEHHA has removed this reference since it does not pertain directly to exposures in fetal or immature animals. As noted earlier, asthma is a complex disease and different types of T cell responses may result with different exposure conditions. Many industrial studies have noted dermal exposure of workers to diisocyanates. Cytokine profiles and T cell responses of sensitized workers could differ depending on the proportion and order of dermal and airborne exposure workers received leading to sensitization. In this sense, the Ban *et al.* study is relevant.

ACC Comment 11:

The key study used for the acute REL (Baur *et al.*, 1994; Vogelmeier *et al.*, 1991) is based on pulmonary responses in human asthmatics with no previous TDI exposure that received a 1h exposure to TDI, the exposure duration used by OEHHA for the determination of an acute REL. OEHHA indicates that there was no NOAEL since 1 of 15 asthmatics experienced a positive airway reaction ($\geq 100\%$ increase in airway resistance) after a 1h exposure to 10 ppb TDI; 1 of the remaining 13 subjects (one dropped out) responded similarly at 20 ppb. The total UF of 30 applied to LOAEL of 10 ppb is inappropriately high.

Use of the full default LOAEL to NOAEL UF of 10 due to the severity of this temporary effect is subjective and overly conservative on several levels. First, the term severe is typically equated with life threatening effects. By equating the responses in asthmatics to severe effects, OEHHA is suggesting that the study investigators were deliberately exposing human volunteers to potentially life threatening conditions. This suggestion is not credible. Second, the response frequency of 7% (1/15) at 10 ppb TDI is clearly approaching the NOAEL for this sensitive population. This response rate approximates the benchmark response (BMR) of 10% commonly used by USEPA to model the benchmark concentration (BMC10) associated with a low incidence of health risk as well as its lower bound confidence limit (BMCL10), which is often preferred in risk assessment over a NOAEL. Benchmark models that meet USEPA acceptability criteria typically have a BMC/BMCL ratio of ~ 1.5 to 2. Thus an UF of 3 provides a more objective yet still health-protective basis for a LOAEL to NOAEL UF.

Response to ACC Comment 11:

OEHHA uses a default LOAEL-to-NOAEL UF = 10 in cases where an asthmatic-like reaction was induced by the exposure. We consider an asthmatic response to be a 100% or greater increase in airway resistance, or a 20% reduction in FEV1. Asthma can sometimes be life-threatening, although in our guidance, a severe effect does not need to be life-threatening. The acute REL is not designed specifically to establish a life-threatening threshold. Rather, the definition of the acute REL is:

“The concentration level at or below which no adverse health effects are anticipated for a specified exposure duration (i.e., 1 hour). RELs are based on the most sensitive, relevant, adverse health effect reported in the medical and toxicological literature. RELs are designed to protect the most sensitive individuals in the population by the inclusion of margins of safety (OEHHA, 1999).” The acute REL is designed for use with infrequent one-hour maximum modeled exposures in the Hot Spots program (OEHHA, 2008).

For the critical study, an asthmatic-like effect occurred in 1 of 15 non-sensitized asthmatic subjects at the lowest concentration, 10 ppb. There is also evidence that sensory irritation occurred in some asthmatic subjects but it is unclear at what dose. If mild sensory irritation in only a few subjects at 10 ppb were the only evident effect from exposure, a LOAEL-to-NOAEL UF = $\sqrt{10}$ might have then been more appropriate.

Regarding a response rate of 7%, OEHHA considers this to be a significant response rate. Ideally, it would have been better if there was a larger number of participants in this study group (e.g., n = 30 to 40 subjects) to get a better idea of the response rate. For benchmark dose modeling, OEHHA favors using a 5% response rate for the BMR because this approximates the lower limit of adverse effect detection likely to occur in typical human epidemiological studies, and in large laboratory animal studies.

One in 15 subjects responding to 10 ppb is a real effect because one in 13 asthmatic subjects had a greater than 100% increase in Raw at 20 ppb. Additionally, the study by Fruhmann et al. (1987), which used the same exposure protocol (and possibly presented data from some of the same group of subjects), provides supporting evidence that the asthmatic reaction at 10 ppb was real. Under their exposure protocol, three of the 15 asthmatic subjects experienced a maximum Raw value greater than 100% of their control value. (Raw was measured in kilopascals per liter per second, kPa.s.L⁻¹.) Another five asthmatic subjects had a maximum increased Raw between 50-100% of their control value, all of which were above 0.35 kPa.s.L⁻¹. (A normal Raw result was considered to be <0.35 kPa.s.L⁻¹ by the authors.) The weakness of this study was that it did not specify at what exposure concentration (10 or 20 ppb) the significant reductions in Raw were measured.

References

Fruhmann G, Baur X, Vogelmeier C, Røommelt H and Pfaller A (1987). Inhalation provocation tests with isocyanates in comparison with methacholine and with skin tests [German]. *Arbeitsmedizin Sozialmedizin Präventivmedizin* 22(4): 94-96.

OEHHA. (1999). *Air Toxics Hot Spots Program Risk Assessment Guidelines. Determination of Acute Reference Exposure Levels for Airborne Toxicants*. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Oakland, CA.

ACC Comment 12:

OEHHA also adds another toxicodynamic UF of 3 ($\sqrt{10}$) to protect children with asthma, bringing the total UF to 30 and the acute REL to 0.3 ppb (10 ppb/30). As described above, the UF for asthmatic children is unwarranted because (a) TDI-induced asthma is a Th1 mediated effect and asthma in children is primarily a Th2 driven process, and (b) the only evidence that TDI exposures might be Th2 driven comes from an a physiological sensitization protocol (topical / tracheal) in an unvalidated mouse model that is irrelevant to hypothetical childhood exposures.

Considering the key studies and estimation of risk for acute exposures, a total UF of 3 provides a more appropriate, yet still health protective, basis for an acute REL of 3ppb (10ppb/3) since there is evidence that the majority of OA cases can be attributed overexposure incidents where TDI concentrations are well above 20 ppb (Ott *et al.*, 2003).

Response to ACC Comment 12:

An intraspecies toxicodynamic default UF of $\sqrt{10}$ was used to address any potential increased sensitivity of children with asthma compared to adults with asthma. If the REL were based on exposures in healthy adults, the toxicodynamic UF would likely have been a full 10.

As discussed in the Response to ACC Comment #9 above, it is unknown how children will react to exposure to TDI when exposed early in life when the immune system is still developing. For risk assessment, it would be inappropriate for OEHHA to assume that children will be less sensitive to the effects of TDI than adults, as the comment implies, and assign a toxicodynamic UF = 1. There are data available that indicates allergic asthma in children is not always a Th2-driven process, and there are data that indicate TDI-induced asthma shows a mixed Th1/Th2-response. Further, as noted in response to comment 9 above, OEHHA views asthma as a disease that disproportionately impacts children. Potential to either induce or exacerbate asthma are considerations in assigning the value of the intraspecies uncertainty factor.

ACC Comment 13:

In Section 6.1.4 (pgs 21-24) OEHHA discusses the decrements in lung function observed by Diem *et al.* (1982) and used as the basis for its 8-hr and chronic RELs. The Panel notes a conservative bias in OEHHA's summary of Diem *et al.* (1982) and that these results are not compared against more recent and longer term occupational exposure studies (e.g., Ott *et al.*, 2000). Considered in total, these occupational exposure studies indicate that the human NOAEL selected by OEHHA (0.9 ppb) is conservative and adequately protects against lung function decrements in the work environment. OEHHA should explain specifically (e.g., in a table) why it did not consider other studies, either alone or in combination with Diem, as the basis for its 8-hr and chronic RELs.

Response to ACI Comment 13:

The 8-hour and chronic RELs are based on work by Diem *et al.* (1982) because they established both a NOAEL (0.9 ppb) and a LOAEL (1.9 ppb) for accelerated loss of FEV1 in TDI workers. Ott *et al.* (2000) only provides a NOAEL for this endpoint. OEHHA does not generally assign REL values based on studies that only provide a NOAEL, otherwise known as a "free-standing" NOAEL. Other longitudinal studies also only determined a NOAEL or the study was not conducted well enough to use as the critical study for a REL.

Another problem with Ott *et al.* (2000) is it was unclear what the average TDI concentration was for workers participating in FEV1 testing. A figure of 234.2 ppb-months is provided but this was not translated into a specific mean concentration of TDI. If one uses the mean years of FEV1 testing of 9.3 years noted in the report, this would roughly translate to a mean concentration of 2.1 ppb. Ott *et al.* (2000) did conclude that exposures ranging up to 5 ppb TWA and where active medical surveillance and exposure monitoring programs were in place, there was little evidence of a relation between exposure to TDI and either FVC or FEV1 decrement. This study, however, relied on some retrospective construction of exposures using different measurement techniques; thus, exposure misclassification could be a problem. The study by Diem *et al.* (1982) found a lower NOAEL (and LOAEL) and was therefore the basis of the REL.

In addition, yearly incidence of sensitization in the Ott *et al.* (2000) workers was listed as 0.7% after 1979, but the workers were not stratified in such a way to determine if there was a concentration of TDI at which sensitization did not occur.

ACC Comment 14:

In its discussion of Diem *et al.* (1982), OEHHA should indicate that when the cumulative TDI dose was expressed as a continuous variable there was no significant association between dose and annual decrements in FEV1. It was only when the dose was expressed as a dichotomous variable (*i.e.*, ≤ 68.2 vs > 68.2 ppb-months) that a marginally significant FEV1 decrement of 12 ml/yr was noted between the two groups. In addition, when the lower exposure group was compared to a yet higher exposure group (> 100 ppm-months), the difference in FEV1 decrement fell to 6 ml/yr. Although Diem *et al.* (1982) indicated that the difference between the two groups was most evident in “never smokers” category, Ott *et al.* (2000) did not see a difference in FEV1 decrement between exposed and unexposed never smokers in their longer-term longitudinal study (17 years) with an average TDI dose of 234 ppb-months. However, in agreement with Diem *et al.* (1982), Ott *et al.* (2000) also observed that there was no relationship between the annual decline in FEV1 and cumulative TDI dose. The results of the five longitudinal studies (reviewed in Ott *et al.*, 2003) indicate that the human NOAEL selected by OEHHA (0.9 ppb) adequately protects against decrements in lungs function (and by extension any sequela of neuroimmune1 sensitization) in the work environment.

Response to ACC Comment 14:

Many of these negative findings described in Comment 14 were included in the REL summary. Regarding the Diem *et al.* (1982) study in particular, we say in both Section 6.1.4 and in Table 13 that linear regression analysis did not find a relationship between a decline in FEV1 and TDI exposure when TDI exposure was treated as a continuous variable. We agree with the ACC and their evaluation of the Ott *et al.* (2000) data indicating that the NOAEL of 0.9 ppb adequately protects workers against decrements in lung function, and should also result in very low incidence of sensitization.

ACC Comment 15:

OEHHA should indicate specifically why it did not consider other longer-term and seemingly stronger longitudinal studies, particularly the study by Ott *et al.* (2000) that was based on the approach used by Diem *et al.* (1982), for its 8-hr and chronic RELs for TDI. At a minimum, these longer-term studies indicate that a subchronic UF is not justified (see below, Section 6.c.).

Response to ACC Comment 15:

The choice of using the Diem *et al.* (1982) study over the Ott *et al.* (2000) study as the critical study for REL derivation is described in Response to ACC Comment 13 above. The default subchronic UF = $\sqrt{10}$ was used in accordance to our guidelines (OEHHA, 2008) because the exposure duration of the prospective study (5 years) was less than

12% of the estimated lifetime for humans (70 years). The default subchronic UF was applied because the critical effect, accelerated decline in FEV₁, may still have been progressing beyond the 5 years of the study period. Five years represents a little over 7% of a worker's lifetime of 70 years. OEHHA would normally apply a default subchronic UF = 10 if the study period were less than 8% of a lifetime. However, in consideration of the generally moderate but variable amount of time required for symptom manifestation, a subchronic UF of $\sqrt{10}$ was applied (rather than a UF of 10).

Regarding exposure time to sensitization, this may occur within weeks of first exposure to TDI, or after many years of exposure. This would argue in favor of genetic predisposition for some individuals, rather than a concentration-related correlation for onset of TDI-induced asthma. Malo et al. (1992) found that nearly 60% of workers exposed to TDI became symptomatic after 5 years of exposure, with a mean latency period of 7.34 years between the start of exposure and the onset of symptoms. However, the time from first sensitization to diagnosis is often delayed so the latency period may be shorter. In any case, a subchronic UF=1 as the commenter suggests using may not be protective of individuals with long latency times beyond 5 years, as has been shown to occur (Malo et al., 1992). Thus, we believe a subchronic UF = $\sqrt{10}$ based on accelerated pulmonary function decline would also be sufficient to protect individuals who become sensitized with lower-level exposure over a longer period of time.

Reference

Malo JL, Ghezzi H, D'Aquino C, L'Archeveque J, Cartier A and Chan-Yeung M (1992). Natural history of occupational asthma: relevance of type of agent and other factors in the rate of development of symptoms in affected subjects. *J Allergy Clin Immunol* 90(6 Pt 1): 937-44.

ACC Comment 16:

For the 8-hr REL (Section 8.2, pg 58), OEHHA uses the same time-adjusted exposure concentration for TDI as it does for the chronic REL. This is inconsistent with OEHHA guidelines and practice as well as available human and animal data. OEHHA inappropriately reduces the worker NOAEL (0.9 ppb) 2-fold by inserting a time-adjustment factor (10/20) that is inconsistent with its Technical Support Document (OEHHA, 2008). OEHHA justifies this conservative approach based on its supposition that TDI may cause respiratory sensitization with only intermittent low-level exposures. However, the studies referenced by OEHHA fail to show that the low level exposures reported by Diem *et al.* (1982) and the NOAEL derived from that study (0.9 ppb) are not sufficiently protective. The decrements in lung function reported in workers by Peters and Wegman (1975) occurred under more severe exposure conditions (i.e., higher (2 – 9 ppb) not lower exposure concentrations) than those described by Diem *et al.* Similarly, and ignoring the fact that there is no generally accepted animal model of

human asthma, the sensitization protocol in mice cited by OEHHA (Matheson *et al.*, 2005a) also employed higher TDI exposure concentrations (20 ppb) in order to achieve a lung pathology consistent with asthma.

Response to ACC Comment 16:

As noted by the ACC, the critical study and the time adjustment for the 8-hour REL is the same as that for the chronic REL below, resulting in the same health value for both the 8-hour and chronic RELs. The standard practice for time extrapolation from an occupational exposure scenario to an equivalent continuous exposure scenario (for the chronic REL) is to multiply the NOAEL by a factor of $10\text{m}^3 / 20\text{m}^3$. The assumptions behind this are that the average worker breathes about $20\text{ m}^3/\text{day}$, and that about half of the air they breathe during the day occurs during work hours when they are most active, that is, 10 m^3 of air. Thus, the time-adjustment extrapolates from an 8-hour working day to a 24-hour chronic exposure, the time duration of the chronic REL. Using the 10/20 time-adjustment is appropriate to protect the general public from the critical effect in the Diem *et al.* (1982) study, accelerated decline in pulmonary lung function as measured by FEV1 (i.e., greater declines in lung function may occur with 24-hour exposure compared to daily 8-hour exposures).

As noted in Section 8.2, for many substances, higher exposure levels are tolerable if the exposures are intermittent versus chronic, thus 8-hr RELs are typically higher than chronic RELs. OEHHA has reconsidered using the same REL value for both the 8-hour and chronic RELs. Both RELs are based on the same study and same finding of accelerated FEV1 loss in the absence of sensitization to TDI, which strongly indicates a chronic inflammatory response in the lung airways of the workers. Evidence for a duration-dependent component for this lesion, as well as data from the companion diisocyanate, MDI, indicates some level of recovery with intermittent daily exposures, such as daily 8-hour exposures, compared with continuous or near continuous exposures, such as chronic exposures. This would support an 8-hour REL not adjusted for continuous exposure. As a result, the proposed 8-hour REL is half that of the chronic REL (i.e., the $10\text{m}^3 / 20\text{m}^3$ factor is removed from the 8-hour REL derivation).

The revised derivation supporting this change in the 8-hour REL reads as such:

*“Repeated daily TDI exposures similar to what would occur in workers may worsen the pulmonary airway lesions as exposure duration increases, as shown in lifetime exposure studies in female rats (Loeser, 1983; Owen, 1984). However, chronic rodent exposure studies with MDI and PMDI found that some level of airway recovery occurs with 6-hour per day exposures compared to exposures of 18 hours per day (Feron *et al.*, 2001). The same would be expected with long-term TDI exposures. This result suggests a lower REL value should be used for continuous chronic exposure, compared to daily 8-hour exposure.*

*C x t studies in TDI-sensitized subjects observed that bronchial responsiveness was neither exclusively concentration- nor duration-dependent (Vandenplas *et al.*, 1993a). A*

duration-dependent component for induction of asthma would also support a chronic REL value that is lower than the 8-hour REL.

Thus, only a time-adjustment of 5 days / 7 days was applied, since daily exposures in the critical study was 8 hours/day, 5 days/week. However, the results also call for a 3-fold subchronic uncertainty factor, since the critical study was only 5 years long. Further details supporting use of individual uncertainty factors are discussed in the chronic REL derivation below.

There is no consensus on the threshold-sensitizing inhalation dose for TDI and some believe there may be no lower limit of exposure at which no workers will be sensitized (Tarlo and Liss, 2002). However, OEHHA considers the 8-hour REL to keep the prevalence of TDI-induced asthma very low. This is due, in part, to very low prevalence rates among workers exposure to 0.9 ppb TDI or lower. The 8-hour REL is 60-times lower than this value. Supporting evidence for 8-hour and chronic RELs also protecting the general public from TDI-induced sensitization is discussed below in the chronic REL derivation.”

References

Feron VJ, Kittel B, Kuper CF, Ernst H, Rittinghausen S, Muhle H, Koch W, Gamer A, Mallett AK and Hoffmann HD (2001). Chronic pulmonary effects of respirable methylene diphenyl diisocyanate (MDI) aerosol in rats: combination of findings from two bioassays. Arch Toxicol 75(3): 159-75.

Loeser E (1983). Long-term toxicity and carcinogenicity studies with 2,4/2,6-toluene-diisocyanate (80/20) in rats and mice. Toxicol Lett 15(1): 71-81.

Owen PE. (1984). The toxicity and carcinogenicity to rats of toluene diisocyanate vapour administered by inhalation for a period of 113 weeks. Addendum report Volume 2. Hazelton Laboratories Europe Ltd., England. Report No. 2507-484/1.

Tarlo SM and Liss GM (2002). Diisocyanate-induced asthma: diagnosis, prognosis, and effects of medical surveillance measures. Appl Occup Environ Hyg 17(12): 902-8.

Vandenplas O, Cartier A, Ghezze H, Cloutier Y and Malo JL (1993a). Response to isocyanates: effect of concentration, duration of exposure, and dose. Am Rev Respir Dis 147(5): 1287-90.

ACC Comment 17:

Other animal studies indicate that neuroimmune sensitization occurs at TDI concentrations at least 20-fold higher than the human NOAEL of 0.9 ppb and that

neurogenic sensitization (TRPA pathway of neuroimmune sensitization) and immunologic sensitization (T-cell pathway of neuroimmune sensitization) exhibit comparable dose-responses. Karol (1983) observed that guinea pigs exposed to TDI vapor (3 hr/day, 5 days/week) required TDI concentrations ≥ 360 ppb to produce both TDI-specific antibodies (a marker for immunologic sensitization) and pulmonary hyperreactivity (a marker for neurogenic sensitization). In mice, Sangha and Alarie (1979) reported that respiratory tract sensory irritation could be observed following 3h exposures to TDI at 23 ppb, but not at concentrations lower than 20 ppb, even upon repeated exposures. Because sensory irritation at 23 ppb was observed in the absence of inflammation (as measured microscopically), the authors suggested that this effect is due to the stimulation by TDI of sensory nerve endings in the respiratory tract (i.e., TRPA-mediated neurogenic sensitization).

Thus, data in humans (Diem *et al.*, 1982; Ott *et al.*, 2003) and animals (Karol *et al.*, 1983; Sangha and Alarie, 1979) indicate that the human NOAEL of 0.9 ppb is sufficiently protective of both immune-mediated and neuroimmune-mediated sensitization. As a result, the 10/20 time-adjustment factor should be eliminated until OEHHA can provide quantitative data to support the inclusion of this additional uncertainty factor in the 8-hr REL for TDI (WHO, 2005).

Response to ACC Comment 17:

As explained in Response to ACC Comment #16, the standard practice for time extrapolation from an occupational exposure scenario to continuous exposure is to multiply the NOAEL by a $10\text{m}^3 / 20\text{m}^3$ factor. This assumes half of a day's 20m^3 of air is taken in during the work hours when workers are most active, that is, 10m^3 of air. Thus, the time-adjustment extrapolates from an 8-hour working day to a 24-hour chronic exposure, the time duration of the chronic REL. A 5 day / 7day factor is also included to extrapolate from 5 days a week to 7 days a week exposure to extrapolate to continuous exposures for the general public. These default assumptions are described in *Technical Support Document for the Derivation on Noncancer Reference Exposure Levels* (OEHHA, 2008).

The higher doses are often used in animal studies to get the desired effect in a shorter exposure period. There are animal studies in which repeated daily exposures were at relevant concentrations for human exposure (20-50 ppb) and resulted in immune system changes (Matheson *et al.*, 2005b; Johnson *et al.*, 2007). In part, this is also because laboratory animals are partly inbred and display significantly less intraspecies diversity compared to humans. Even so, OEHHA notes that the acute exposure study by Sangha and Alarie (1979) shows that a change in respiratory rate occurred at 23 ppm. This is, in fact, around the same concentration that resulted in sensory irritation and reduced pulmonary function in non-sensitized asthmatic human subjects (Baur *et al.*, 1994; Vogelmeier *et al.*, 1991; Fruhmman *et al.*, 1987). Finally, the Sangha and Alarie study was an acute study, and not particularly relevant for derivation of the repeated 8-hour REL and the chronic REL.

References

Baur X, Marek W, Ammon J, Czuppon AB, Marczynski B, Raulf-Heimsoth M, Roemmelt H and Fruhmans G (1994). Respiratory and other hazards of isocyanates. *Int Arch Occup Environ health* 66(3): 141-52.

Johnson VJ et al. (2007). Inhalation of toluene diisocyanate vapor induces allergic rhinitis in mice. *J Immunol* 179:1864-1871.

Matheson JM, Johnson VJ, Vallyathan V and Luster MI (2005b). Exposure and immunological determinants in a murine model for toluene diisocyanate (TDI) asthma. *Toxicol Sci* 84(1): 88-98.

Vogelmeier C, Baur X and Fruhmans G (1991). Isocyanate-induced asthma: results of inhalation tests with TDI, MDI and methacholine. *Int Arch Occup Environ Health* 63(1): 9-13.

ACC Comment 18:

For the 8-hr and chronic RELs (Sections 8.2 and 8.3, pgs 58-59), OEHHA uses a subchronic UF of $\sqrt{10}$ because the Diem et al. default subchronic UF of $\sqrt{10}$ based on the 5 year exposure duration reported by Diem et al. (1982).

Incorporation of this UF is inappropriate. Studies with comparable mean exposure durations but with maximum exposure durations of 20-30 years (Ott et al., 2000; Bodner et al., 2001) support the Diem et al. (1982) NOAEL of 0.9 ppb indicating that a 3-fold lower NOAEL will not afford greater protection against TDI-induced asthma. In addition, data provided by Ott et al. (2000) show that the longer the duration of TDI exposure, the lower the risk of developing TDI-induced asthma. Ott noted that the annual rate of TDI-induced asthma is highest during the first 11 months of exposure (7 cases/yr), falls to 3.5 cases/yr during months 12-35, to 1.5 cases/yr during months 36-59, and to < 0.5 cases/yr at 60 months. Ott further states that these rates are conservative since reported asthma cases were not confirmed by specific inhalation challenge (SIC). Using data reported by others, Ott indicates that the annual rates would be about 3-fold lower if the suspected cases of TDI-induced asthma were subjected to SIC. Finally, and of particular note, a conditional logistic regression analysis was performed by Ott et al. (2000) to evaluate potential risk factors for developing asthma induced by TDI. One of the statistically significant ($p < 0.05$) risk factors was the duration of previous exposure to TDI, which was inversely related to risk (i.e., the longer the exposure duration, the lower the risk of developing TDI-induced asthma).

Thus, in the case of TDI, the data indicate that the incidence of TDI-induced asthma observed in studies with a mean exposure duration of 5 years approximates the incidence of toxic effects one would expect to see in chronic exposures to toxicants. This position is consistent with OEHHA's claim that the relatively rare cases of TDI-

induced asthma associated with TDI concentrations reported in contemporary occupational settings are likely occurring in genetically sensitive individuals. Consequently, a default subchronic UF of 3 is not required.

Response to ACC Comment 18:

This comment is similar to Comment #15 above. Please refer to the Response to ACC Comment #15. OEHHA is mandated to develop risk assessment guidelines under the Air Toxics Hot Spots program (pursuant to Health and Safety Code Section 44360. We have used our public- and peer-reviewed guidelines for evaluating the value to apply for our uncertainty factors.

Briefly, the default subchronic UF = $\sqrt{10}$ was used because the critical effect, accelerated decline in FEV₁, may still progress beyond the 5 years of the study period. Regarding time to sensitization, one study found that nearly 60% of workers exposed to TDI became symptomatic after 5 years of exposure, with a mean latency period of 7.34 years between the start of exposure and the onset of symptoms (Malo et al., 1992). Another study found the average duration of exposure to isocyanates ranged between 8 and 15 years before onset of asthma (Mapp et al., 1988). It was noted that the average duration of symptoms for these subjects before diagnosis was between two and five years, showing that diagnosis was often delayed. OEHHA believes these data support a subchronic UF for the 8-hour and chronic RELs.

We could not find the information claimed by the ACC that Ott et al. (2000) determined the number of asthma cases per year based on employment time at the TDI facility. Thus, we cannot confirm the comment that induced asthma drops to <0.5 cases/yr at 60 months of exposure.

Reference

Mapp CE, Boschetto P, Dal Vecchio L, Maestrelli P and Fabbri LM (1988). Occupational asthma due to isocyanates. *Eur Respir J* 1(3): 273-9.

ACC Comment 19:

For the 8-hr and chronic RELs, OEHHA applied a 10-fold intraspecies toxicokinetic (TK) UF (Sections 8.2 and 8.3, pgs 58-59) to account for genetic differences found in the relatively small fraction (3% – 8%; Table 13, pg 41) of TDI-exposed workers that develop occupational asthma. This UF is inappropriate. Although OEHHA does not report the TDI concentrations to which a small fraction of genetically different workers (Table 16) with TDI-induced asthma were exposed, one of the studies listed there (Piiirila *et al.*, 2001) reported TDI levels of 16 – 76 µg/m³ (2 – 11 ppb), levels not dissimilar from those one might expect in contemporary workplaces (i.e., ACGIH 8 h TWA of 5 ppb) or levels reported in the occupational studies listed in

Table 13. Because the number of workers in the occupational studies (Table 13) was generally greater than the number of workers evaluated in the genomic studies (Table 16), it is likely that the two populations exhibited a similar spectrum of genetic differences and sensitivities to TDI-induced asthma. Thus, the NOAEL for TDI induced asthma of 0.9 ppb established by OEHHA based on the occupational study by Diem *et al.* (1982) will be protective of both genetically sensitive and non-sensitive workers. OEHHA should provide data indicating that a TDI concentration 10-fold lower than 0.9 ppb is needed to protect genetically sensitive populations; the use of an odds ratio for this purpose is inappropriate. In the absence of such data, a 10-fold intraspecies TK UF for genetic differences is unwarranted and should be reduced to 1. If OEHHA chooses to ignore this recommendation and use an UF greater than the standard default of $\sqrt{10}$, it needs to provide quantitative data to support its decision as outlined in the World Health Organization report (WHO, 2005).

Response to ACC Comment 19:

OEHHA is mandated to develop risk assessment guidelines under the Air Toxics Hot Spots program (pursuant to Health and Safety Code Section 44360). We have used our public- and peer-reviewed guidelines for evaluating the value to apply for our uncertainty factors. An intraspecies toxicokinetic uncertainty factor = 10 was applied to account for the up to 10-fold greater susceptibility to diisocyanate induced asthma in workers with specific gene variants associated with metabolizing enzymes including GSTM1, GSTP1, EPHX, and NAT1. Examples of genes include, but are not limited to, genes involved in immune regulation, inflammatory regulation, and antioxidant defense. The range in mean Odds Ratio (OR) values in Table 16 was 1.89 to 10.36 associated with polymorphisms in these enzymes.. Note that this range is based on mean OR values. The upper 95% confidence interval on the ORs ranged as high as 69.9. Thus, the intraspecies toxicokinetic UF = 10 chosen was based on the high end for mean ORs. A similar method was used recently in determining the intraspecies UF for the 8-hour and chronic benzene RELs based on gene variability ORs, so this is not a novel methodology. Another consideration is that the ORs were determined in worker populations. Often, they exhibit the “healthy worker effect” in that an unintentional (or even intentional) selection process could have occurred that kept more vulnerable members of the general population away from exposure to TDI. This could mean that the variability in gene variants that increase risk of sensitization may be greater in the general population. Therefore, we believe that we are not overly conservative in applying an intraspecies toxicokinetic uncertainty factor = 10.

ACC Comment 20:

For the 8-hr and chronic RELs, OEHHA (Sections 8.2 and 8.3, pgs 58-59) uses an intraspecies toxicodynamic (TD) UF of 10 to account generically for hypothetical differences in the way TDI may affect different age groups, and specifically for the purported greater sensitivity of infants and children to TDI- induced decrements in lung

function. An intraspecies toxicodynamic UF of 10 is not supported by scientific evidence indicating children are less sensitive to TDI-induced lung decrements. OEHHA is already aware (pg 57) that if children were exposed to TDI by inhalation, they would receive lower tracheobronchial regional doses than adults. In addition, as indicated by the Panel above, children are less sensitive to lung decrements associated with TDI-induced asthma because TDI asthma is primarily a Th1 driven process, while childhood asthma is a Th2 driven process. Again, although an UF of 1 is consistent with the available data, if OEHHA uses an UF greater than the default value ($\sqrt{10}$), it needs to provide quantitative data to support its decision (WHO, 2005).

Response to ACC Comment 20:

OEHHA is mandated to develop risk assessment guidelines under the Air Toxics Hot Spots program (pursuant to Health and Safety Code Section 44360). We have used our public- and peer-reviewed guidelines for evaluating the value to apply for our Uncertainty Factors. We applied an intraspecies toxicodynamic (TD) UF = 10 to account for pharmacodynamic variability among pregnant women and their fetuses and among infants, children, and adults. As noted in Table 16 of our document, increased odds of developing isocyanate-induced asthma was associated with a number of genes related to toxicodynamic variability. Examples of genes include, but are not limited to, genes involved in immune regulation, inflammatory regulation, and antioxidant defense. Although the critical effect was in an adult worker population, the potential greater sensitivity for lung function impairment in the developing lungs of infants and children would also support an intraspecies TD UF of 10.

There is no evidence that children are less sensitive to TDI-induced sensitization and pulmonary lung decrements, as the comment asserts. The development of asthma from exposure to TDI is complex and it is not well known what the mechanism for TDI-induced asthma is in adults, much less children. As discussed above in Response to ACC Comments #8 and #9, TDI-induced asthma often appears to be a mixed T cell response in which both Th1 and Th2 processes are involved. This has also been shown in murine animal models for diisocyanate-induced sensitization. Because we suspect there is additional susceptibility of children exposed to TDI, we use the default intraspecies toxicodynamic UF = 10 as described in our Noncancer Technical Support Document (OEHHA, 2008).

OEHHA notes that differences in tracheobronchial regional doses between children and adults are a toxicokinetic factor, not a toxicodynamic factor as suggested in the comment. The tracheobronchial minute volume (MV) to surface area (SA) is slightly lower overall in children when compared to adults, as the ACC points out. This is the region of the airways most sensitive to effects from TDI exposure. This toxicokinetic difference would result in lower tracheobronchial regional doses in children. So it was appropriate in the case of the acute REL to use an intraspecies toxicokinetic UF = 1 because the critical effect was measured in a group of asthmatic non-TDI-sensitized adults. However, it is not appropriate to use this same intraspecies toxicodynamic UF for the repeated 8-hour and chronic RELs. The toxicogenomics data for diisocyanates

show gene variants associated with increased sensitivity up to 10-fold greater in workers developing diisocyanate-induced asthma. These findings address long-term repeated exposures resulting in diisocyanate-induced asthma and are only applicable to the 8-hour and chronic REL derivations.

Responses to Comments Received from PFA

PFA Comment 1:

The Polyurethane Foam Association (“PFA”), a not-for-profit trade association representing U.S. manufacturers of flexible polyurethane foam (“FPF”) and their suppliers of chemical raw materials, provides these comments on the 2014 Public Review: Toluene Diisocyanate Reference Exposure Levels document by Office of Environmental Health Hazard Assessment (“OEHHA”). OEHHA is considering alterations to the RELs for acute and chronic exposures to TDI. However, REL revisions are unnecessary because the current REL (0.01 ppb) established by OEHHA already controls TDI emissions effectively and protects against the health and safety concerns raised by OEHHA.

Response to PFA Comment 1:

The OEHHA REL revisions are updated occasionally for individual chemicals to include new information that may affect the REL values. However, the current revisions also take into account our new guidance in the Noncancer Technical Support Document (OEHHA, 2008) which specifically includes consideration of greater sensitivity of early-in-life exposures. This is particularly true for chemicals that have their critical effects on the respiratory system, such as TDI. Thus, the current RELs for TDI are not necessarily protective for infants and children and need to be updated. Also as part of the new OEHHA Guidelines, we are now deriving 8-hour RELs for repeated 8-hour exposures, primarily for exposure to offsite workers or children attending schools located near sources.

PFA Comment 2:

Further, the research cited by OEHHA in the July 2014 document is outdated in several instances. Recent peer-reviewed research and governmental studies on the respiratory impact of TDI on consumers, workers whose jobs involve using TDI, and community populations near manufacturing sites where TDI is used in flexible polyurethane foam production, demonstrate that revisions to the RELs are unnecessary. Also, there is no reliable evidence that infants, children and others who may be particularly susceptible to

TDI sensitivity will ever be exposed to TDI from use of products containing flexible polyurethane foam or from possible concentrations of TDI in the air near FPF manufacturing locations.

Response to PFA Comment 2:

OEHHA has added more recent studies in response to other commenters. This comment is better addressed below in other comments in which the references are cited.

PFA Comment 3:

Background

As background information, open cell flexible polyurethane foam differs from other types of polyurethane foams, coatings, adhesives and sealants in its applications and safe use in consumer products. Open cell FPF is a key component in many consumer, medical and industrial products including adult and infant mattresses, upholstered furniture, automotive seating and protective interior vehicle padding, many types of pillows, medical restraints and orthopedic supports, wound dressings, sponges, industrial filtration, sports equipment, carpet padding and various types of specialized packaging for delicate instruments, food produce and small electronics.

There are other types of polyurethane products, such as certain adhesives, sealants, coatings, and spray products that are not cured until they are used. These types of products are typically applied in the field, and not in a manufacturing facility. FPF products are always cured in a manufacturing facility prior to further use, and there is no opportunity for exposure to unreacted TDI raw materials or other isocyanates in finished FPF end-products.

While TDI may be a component in certain prepolymer-based uncured polyurethane products, the great majority of all TDI used in California is consumed in the manufacturing of FPF. TDI is one of three key raw materials used to produce FPF (the others are polyol and water). TDI reacts efficiently with water and polyol, creating a chemical reaction which consumes essentially all of the TDI to form FPF polymers. Tests show that during the reaction, with each metric ton of foam produced, no more than 50 grams of TDI remain after the initial reaction. During curing, any trace of remaining TDI is managed through controlled production ventilation systems. Numerous tests demonstrate that after the curing process is complete, TDI levels are non-detectable and, as a result, there is very little potential for exposure from normal use of cured consumer products containing FPF materials. Citizens in California communities, including particularly vulnerable populations of children and senior citizens, are not at risk for TDI exposure from FPF products.

This conclusion has been verified by:

- Peer-reviewed research by the International Isocyanates Institute which found no available TDI in finished polyurethane foam products and no opportunity for TDI exposure (1,2).
- Studies by foam producers and others which came to the same conclusions as those of the International Isocyanates Institute (3,4).
- An extensive report, published by California's Air Resources Board Research Division, which stated that "the absence of detectable TDI emissions in the screening tests indicates that release of TDI to air from common residential products is negligible (5)."
- A study published in *Applied Occupational and Environmental Hygiene* that found that it is not likely that TDI would be released from three-day post-production polyurethane foams in amounts likely to produce air concentrations of concern (6).

1 Scott M. Arnold, Michael A. Collins, Cynthia Graham, Athena T. Jolly, Ralph J. Parod, Alan Poole, Thomas Schupp, Ronald N. Shiotsuka, Michael R. Woolhiser, "Risk Assessment for Consumer Exposure to Toluene Diisocyanate (TDI) Derived From Polyurethane Flexible Foam," *Regulatory Toxicology and Pharmacology*, 64 (2012) 504-515.

2 M A Collins, E. Vangronsveld, S. Berckmans, P. Maddison, M. Spence, "Free Monomer in PU Products, Global Isocyanates Limited, presentation at the Korean Polyurethane Society, Everburg, Belgium, June 2009.

3 Rocco P. Triolo, Ph.D., "Analysis For Free TDI in Flexible Polyurethane Foams," presentation at Polyurethane Foam Association Technical Conference, Point Clear, Alabama October 1992.

4 "Assessment Of Potential Health Risks Resulting From Chemical Emissions From New Bedding Sets," Research Triangle Institute, December 1995.

5 Thomas J. Kelly, "Determination Of Formaldehyde And Toluene Diisocyanate Emissions From Indoor Residential Sources," report for Air Resources Board Research Division, California Environmental Protection Agency, Contract No. 93-315, November 1996.

6 J. M. Hugo, M. W. Spence, and T. D. Lickly, "The Determination Of The Ability Of Polyurethane Foam To Release Toluene Diisocyanate Into Air," *Applied Occupational and Environmental Hygiene*, June 2000, 15:6, 512-519.

Response to PFA Comment 3:

We have revised Section 6.2 (Chronic Toxicity to Infants and Children) to include the suggested studies that examined the airborne emission of TDI from consumer products

made with TDI, and included studies that used solvent extraction methods to solubilize and remove any free TDI in consumer products made with TDI. The revised section now reads:

“No studies of inhalation exposures to TDI among children were located and it is unknown how early-in-life exposures to TDI would affect the immature immune system. However, it has been postulated that early life exposure to TDI may occur through inhalation and dermal contact with polyurethane products (Krone et al., 2003). Strachan and Carey (1995) found independent associations between severe wheeze and the use of non-feather bedding, especially foam pillows (odds ratio 2.78; 95% C.I. 1.89 to 4.17), among children with 12 or more wheezing attacks in the previous 12 months. The authors speculated that volatile organic compounds could be off-gassing from the foam pillows. However, other researchers found that there is increased exposure to house dust mite allergens from synthetic pillows compared to feather pillows and that this may explain the increased asthma symptoms (Crane et al., 1997).

In addition, two studies did not find emission of detectable levels of free TDI from consumer products that were made with TDI (e.g., carpet padding mattress and furniture foam, varnishes and sealants) has not been found (Hugo et al., 2000; CARB, 1996). Krone et al. (2003) applied semiquantitative tests (i.e., wipe test and extraction with dimethyl sulfoxide) for isocyanate to polyurethane products, including mattresses, mattress pads, sofa padding, carpet pads and pillows, and detected free isocyanate in these consumer products. It was suggested that isocyanate may be available to dissolve in skin oils upon dermal contact. A similar study by Vangronsveld et al. (2013) used various solvent systems and detection methods to extract free TDI from flexible polyurethane foam. A toluene-based extraction technique was deemed the most consistent and resulted in µg/g levels of free TDI extracted from the foam. The authors hypothesized 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.”

Among the references that the commenter suggested adding, we included the reference 5 (CARB, 1996) and the published report that resulted from the industry presentation in reference 2 (Vangronsveld et al., 2013). We did not have access to the presentations in references 3 and 4, but they appear to be similar to work performed by Hugo et al. (2000) and Vangronsveld et al. (2013), which we did include. We did not include the Arnold et al. (2012) reference because this was essentially a review of the literature used to derive the cancer risk from exposure to products containing TDI.

PFA Comment 4:

Potential TDI Exposure in Communities Near FPF Manufacturing Facilities

In contrast to the OEHHA-cited 2002 study, “Clinical Findings For Residents Near A Polyurethane Foam Manufacturing Plant,” authored by Darcey, Lipscomb, Pate, Cherry, and Bernstein, members of the same research team were involved in a more recent longterm follow-up study conducted in cooperation with the North Carolina Department of Health and Human Services (“NCHHS”) under contract with the United States Agency for Toxic Substances and Disease Registry (ATSDR). The comprehensive follow-up research (7) examined possible adverse health effects of TDI on people living near FPF manufacturing plants that use TDI. After taking 80 different air quality samples, NCHHS determined that no TDI was found, except for one reading of 1 part per trillion, an alleged detection that may have been outside reliability tolerances for the equipment. NCHHS also performed 350 blood tests on citizens living in the nearby community and found only one person who had antibodies for TDI. That person reported recently using a polyurethane deck sealant during a home project. The study’s conclusion noted that “[o]verall, we did not find a connection between living near a TDI releasing plant and having asthma or symptoms like asthma (breathing problems)” and “[w]e did not find a scientific connection between respiratory problems and exposure to TDI.”

Independent third-party testing for potential ambient TDI concentrations in and around foam manufacturing plants in North Carolina, commissioned by FPF manufacturers, is congruent with the findings of the NCHHS study. These individual tests paralleled and followed the protocol of the NCHHS study. Following the protocol, with enhancements such as wind monitoring to increase accuracy, the third-party tests found no detectable TDI in the sampling areas near FPF production sites. The tests were conducted in the field for a total of 63 days over twelve weeks and encompassed 10 different locations. A paper summarizing the study is appended to this letter as Attachment 1.

The U.S. Environmental Protection Agency (“EPA”) conducted a study in 2009 of air toxics emissions (TDI) near schools that further substantiates the above-mentioned results. After taking air samples near 7 school locations, the EPA determined that the samples it collected did not, “indicate the presence of [TDI] at levels of health concern (8).”

7 Lynn C. Wilder, Ricky L. Langley, Dan C. Middleton, Kathleen Ernst, Zana L. Lummus, Robert P. Streicher, Douglas S. Campbell, Wendy A. Wattigney, Jonathan A. Bernstein, David I. Bernstein, Steve M. Dearwent, “Communities Near Toluene Diisocyanate Sources: An Investigation Of Exposure And Health,” *Journal of Exposure Science & Environmental Epidemiology*, November/December 2011, 21(6):587-94.

8 “Assessing Outdoor Air Near Schools,” U.S. Environmental Protection Agency, 2009 (Reports listed by school).

Response to PFA Comment 4:

We have included reference #7 suggested by the commenter and revised the paragraph briefly discussing potential exposure to neighborhoods near polyurethane manufacturing facilities. The paragraph now reads:

“Occupational exposure to TDI may occur through inhalation and dermal contact during its production or use. 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 suggests extremely low (one part per trillion) to no current TDI exposures to nearby residents (Wilder et al., 2011).”

Regarding reference #8, this appears to be a program started in 2009 by US EPA. As part of their new air toxics monitoring initiative, US EPA, state and local air pollution control agencies monitored the outdoor air around schools for hazardous air pollutants. The Clean Air Act includes a list of 187 of these pollutants. US EPA selected schools after evaluating a number of factors including results from an US EPA computer modeling analysis, the mix of pollution sources near the schools, results from an analysis conducted for a recent newspaper series on air toxics at schools, and information from state and local air pollution agencies. Key pollutants were monitored, which included TDI, MDI and HDI. Certain schools were selected because they were near facilities that used diisocyanates in manufacturing processes (<http://www.epa.gov/schoolair/OleanMiddl.html>), but as in the case of Olean Middle School cited here, for example, no detectable TDI or other diisocyanates have been found.

OEHHA thanks the commenter for including Attachment 1, which is supplementary monitoring data conducted independently from the ATSDR monitoring program. However, it appears to be a non-peer reviewed industry report that essentially presented similar findings as the ATSDR report, so it was not included in the REL summary.

PFA Comment 5:

Potential Instances of Occupational Asthma Among FPF Workers

In contrast to older studies cited in the July, 2014 OEHHA Public Review Draft related to potential occupational asthma and possible TDI sensitivity among factory workers, recent industry surveys regarding the frequency of reported occupational asthma among FPF factory workers provide a more focused, contemporary view of industry success in mitigating potential exposure pathways in the FPF production workplace. Survey results, summarized in a poster presented by PFA at the International Isocyanates and Health Conference held in April, 2013, are appended as Attachment 2.

The PFA poster emphasizes that there is little potential for worker exposure in proximity to the production process where the reaction is taking place. These areas are typically monitored, have restricted access, and have safeguards in place to prevent worker exposure. PFA surveys examined the number of cases of self-reported and medically

confirmed incidence of occupational asthma (OA) among thousands of FPF production workers over more than 20 years. The survey results substantiate the effectiveness of manufacturing safeguards including work practices, and safety and technological investments made by FPF manufacturers. The surveys indicate a very low incidence of reported occupational asthma among FPF workers. In fact, the historical incidence of reported occupational asthma (less than 2% of FPF production area workers) is well below the incidence of asthma in the U.S. adult population.

The PFA OA survey is updated periodically. A recent update providing reports of occupational asthma among 662 workers at 49 FPF manufacturing plants during 2012 and 2013 indicated just one case of self-reported occupational asthma, and there were no cases that were medically diagnosed.

The survey results speak well for the safety of existing limits on TDI exposure and the ability of FPF production facilities to control the incidences of exposure to TDI in the air through aggressive ventilation and abatement technologies, frequent personal monitoring, and use of personal protective equipment (PPE) in areas with the potential for greater TDI concentrations.

Response to PFA Comment 5:

In the most recent 2008-2011 update provided in Attachment #2, the results show respondents reported an aggregate total of 11 cases (about 1% of the production workforce) of unconfirmed, self-reported occupational asthma over the four year period, 2008 – 2011. Six cases (about 0.6% of the production workforce) were confirmed via medical diagnosis over the same four-year period.

These data indicate that about 1,110 personal monitoring tests were conducted over the four-year period among 1,037 reported production area employees. A number of companies indicated that area monitoring is also used in their plants. The responses concerning average ambient concentrations of TDI varied. Seventeen plants reported average TDI concentrations in production areas to be between 0.045 ppb and 12 ppb. However, 11 of the 17 reporting plants indicated an average ambient concentration of less than 1.8 ppb. Twenty-one plants did not report average or greatest TDI concentrations. The response to greatest concentration in the ambient air also varied greatly. Seventeen plants reported greatest concentrations of TDI to be between 0.375 ppb and 61 ppb. Twelve of the 17 reporting plants had greatest concentrations that were less than 10 ppb.

Some respondents noted that reporting ambient concentrations of TDI in the production area did not necessarily relate to the purpose of the survey, which was to determine the prevalence of occupational asthma among FPF production workers. Having concentrations of TDI in certain production areas did not necessarily mean there was worker exposure and having higher concentrations in certain areas did not necessarily mean that control technologies were not effective in helping to reduce potential worker

exposure. For example, workers at the plant reporting a measured TDI concentration of 61 ppb are fitted with full-face respirators and breathe only clean air.

OEHHA notes that this is a non-peer reviewed study that has not been published in the open scientific literature. It appears to include useful recent information relating to sensitization rates with exposure. However, study drawbacks included self-reported symptomology. The study is unclear as to the rate of workers dropping out due to symptoms of sensitization, and then never recorded. This has been a problem in other studies cited in the REL documents for TDI and MDI. Also, monitoring data was not recorded at a number of the facilities and does not always relate to actual worker exposures. If these data are eventually published in a peer-reviewed journal, OEHHA could then consider it in the TDI REL summary.

PFA Comment 6:

Conclusion and Recommendations

Regulatory decisions affecting potential exposure to raw materials in manufacturing, as well as safeguards related to the use of finished products, should be based on good science and a thorough understanding of product characteristics, applications and their differences, along with factual information about the presence or absence of emissions of concern from finished products.

While PFA appreciates “hot spot” mandates that affect OEHHA review initiatives, we are not aware of any scientific information that indicates a need to lower the REL for TDI in the FPF workplace, or a need to impose any additional restrictions on the emissions of TDI from FPF manufacturing sites. Furthermore, there is no reliable research that indicates any potential for consumer exposure to TDI from cured FPF products.

Response to PFA Comment 6:

As noted in Response to PFA Comment 1, the OEHHA REL revisions are updated occasionally for individual chemicals to include in new information that may affect the REL values. The current revisions take into account our guidance in the Noncancer Technical Support Document (OEHHA, 2008), which specifically includes consideration of greater sensitivity of early-in-life exposures. This is particularly true for chemicals that have their critical effects on the respiratory system, such as TDI. Thus, the current RELs for TDI are not necessarily protective for infants and children and need to be updated. Also as part of the new OEHHA Guidelines, we are now deriving 8-hour RELs for repeated 8-hour exposures, primarily for exposure to offsite workers.

We have included more studies concerning air emissions and extraction of TDI from consumer products, although we note that the Hot Spots Program is primarily

concerned with facility release of airborne emissions of chemicals that may impact nearby neighborhoods and offsite workers.