DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR TOLUENE DIISOCYANATE AND METHYLENEDIPHENYL DIISOCYANATE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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Peer reviewers for the third pre-public comment draft of the Toxicological Profile for Toluene Diisocyanate and Methylenediphenyl Diisocyanate were:

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Comments provided by Peer Reviewer #1:

COMMENT 1: Regarding Chapter 1, the Reviewer noted **"**The tone of this chapter is factual and presents the information in a non-technical style, although the discussion of isomers in answer to the question "What are TDI and MDI?" may be beyond what the lay public can understand. Perhaps the wording could say "Commercial-grade TDI is made up of an 80:20 mixture of two similar forms of TDI. MDI consists of several different forms as well." In addition, perhaps the first instance of the word hydrolysis in this chapter (in answer to the question "Where are TDI and MDI found?") can be followed with the phrase "breakdown by water" in parentheses." The Reviewer also noted "The answers to the questions in this chapter adequately address the concerns of the lay public."

RESPONSE 1: *The text was revised to indicate that there are several forms of TDI and MDI, which are called isomers. The two most common isomers of TDI are 2,4-TDI and 2,6-TDI and the most common isomer of MDI is 4,4'-MDI.*

COMMENT 2: Regarding Section 2.2, the Reviewer noted "For TDI, the following should be added to the statement on page 12 that three studies examining workers at polyurethane foam manufacturing facilities found a suggestive association between work in the facility and lung cancer in female workers: "but an association with diisocyanate exposure was not established."

RESPONSE 2: *A statement was added that none of the studies provided quantitative estimates of TDI exposure.*

COMMENT 3: Regarding Section 2.2, the Reviewer noted "Also on page 12, the discussion of clear evidence of carcinogenicity in rats and female mice orally exposed to TDI is not likely to be of concern to humans, as the exposure route of oral gavage administers the TDI in an organic solvent directly to the acidic environment of the stomach, and this process greatly increases the likelihood that TDA is formed (as discussed further below in my comments on Section 3.2)."

RESPONSE 3: *The first sentence of the referenced paragraph clearly states that the general public is unlikely to be exposed to TDI via ingestion.*

COMMENT 4: Regarding the LSE tables and figures, the Reviewer noted "The LSE tables and figures are complete and self-explanatory (with help from the Users Guide). I agree with the categorization of "less serious" and "serious" effects, except for one case. In Table 3-1, under Acute Exposure, the 45% decrease in body weight gain in the study by Tyl *et al.* (1999a) is a "serious" effect, whereas the 38% decrease in body weight gain in the same study by Tyl (one effect for the dose-range-finding study, the other for the corresponding developmental toxicity study) is a "less serious" effect. Is there a threshold between 38% and 45% for which you think a decrease in body weight becomes serious? Or should the 45% decrease in body weight be considered a "less serious" effect, similar to all other instances of decreased body weight in the LSE tables?"

RESPONSE 4: *In the Tyl et al. (1999a) range finding study, there was a 27% decrease in body weight at 1 ppm, which was considered a serious LOAEL; the 45% decrease in body weight gain in the main study was also considered a serious LOAEL. The LSE table and corresponding text was corrected.*

COMMENT 5: Regarding Figure 3-2, the Reviewer noted "the y-axis is labeled as ppm, but all concentrations for MDI are reported as mg/m^3, not ppm. Please change the axis label to mg/m^3, or convert all concentrations to ppm."

RESPONSE 5: *The unit was corrected to mg/m^3.*

COMMENT 6: Regarding the discussion of respiratory effects of TDI in humans, the Reviewer noted "this section doesn't identify many study limitations. Although it notes that some studies are limited by inclusion of workers with asthma-like respiratory symptoms, other limitations, such as the general limitations of cross-sectional studies and how they cannot establish cause-and-effect due to a lack of temporality, are not discussed. The section also doesn't indicate the reliability of the studies, which is important given the mixed results of the longitudinal studies of effects on lung function. Similarly, for MDI, there are few study limitations noted."

RESPONSE 6: *Section 3.2 of the profile is written as an authoritative review of the available data for a particular end point. Although not discussed in the profile, the study limitations were considered during the evaluation of the individual studies and the preparation of the health effect summary.*

COMMENT 7: Regarding the discussion of respiratory effects of TDI and MDI in animals, the Reviewer notes "there is no discussion of relevance to humans, study limitations, or study reliability."

RESPONSE 7: *See the RESPONSE to COMMENT 6.*

COMMENT 8: Regarding Section 3.2.2, the Reviewer noted "the text does not discuss study limitations or reliability for non-cancer effects, nor does it discuss the human relevance of the results of the animal studies."

RESPONSE 8: *See the RESPONSE to COMMENT 6.*

COMMENT 9: Regarding Section 3.2, the Reviewer noted "For most health effect endpoints, the data are sparse. In general, besides the few issues noted above, the data are adequately described, the text includes appropriate conclusions, and appropriate NOAELs and LOAELS were identified. In addition, the animal data were used to draw support for human respiratory effects, which is valid, but the text still needs to address relevance to humans."

RESPONSE 9: *The discussion of the relevance to humans is presented in Section 2.2 of the profile.*

COMMENT 10: Regarding the discussion of children health, the Reviewer noted "There are no data or general issues relevant to child health that have not been discussed in the profile but should be."

RESPONSE 11: *No revisions were suggested.*

COMMENT 12: The Reviewer identified several typographical errors in Section 3.2:

- page 23, line 16 notes that "Figure 3-x" shows a range for the upper bound of estimated excess cancer risks. Which figure is this supposed to be? I don't see this information in Figures 3-2 or 3-3.
- page 25, line 13, "couth" should be "cough"
- page 26, line 10, "have found" should be "have been found"
- page 32, line 30, "208" should be "2008"
- page 33, line 16, "was observed" should be "were observed"
- page 38, line 24, "uticarial" should be "urticaria"

RESPONSE 12: *The suggested revisions were made.*

COMMENT 13 (page 38, lines 23-24): The Reviewer noted "I don't think that breathing difficulties and facial urticaria represent an ocular effect."

RESPONSE 13: *The case report of facial urticaria was moved to the dermal effects section.*

COMMENT 14 (page 39, lines 20-34): The Reviewer noted "It should be noted that the authors (Le Quesne *et al*.) supposed that the exposure was limited to TDI, but a wide range of other chemicals were present and exposure concentrations to TDI or these other chemicals were not measured. In addition, the authors did not appropriately acknowledge the possible neurological effects of low oxygen, as well as high levels of carbon monoxide or other gases, that may be generated during a fire."

RESPONSE 14: *Statements were added that exposure to other chemicals or carbon monoxide is possible; it was also noted that there was a potential for anoxia. In tests of long-term health effects, the exposed firemen were compared to unexposed firemen, which controlled for some potential confounders that may result from extinguishing a fire.*

COMMENT 15 (page 40, lines 1-16): The Reviewer noted "Severe limitations of the study by Singer and Scott (1987) should be pointed out. The study lacked a control group, had only 3 cases, used variable test methodology between evaluations, and there was a significant delay between exposure and evaluation. Comparison of results 16 months post-exposure to those from two months post-exposure in the same exposed individual with no data from unexposed controls does not allow one to make any conclusions regarding an effect of TDI exposure in this study."

RESPONSE 15: *A statement was added that the small number of subjects, lack of a control group, and small magnitude of effect limits the interpretation of the results.*

COMMENT 16 (page 42, line 5): The Reviewer noted "should "mixtures" be "isomers"?"

RESPONSE 16: *The workers were exposed to several diisocyanate compounds; thus, the term "mixtures" is correct.*

COMMENT 17 (page 48, line 22): The Reviewer commented "there should be a comma and a space between "fibrosarcomas" and "pancreatic""

RESPONSE 17: *The suggested revision was made.*

COMMENT 18 (page 48, lines 25-26): The Reviewer commented "Important additional limitations related to the test material should be stated. Page 55 of this Toxicological Profile notes that Seel *et al*. (1999) showed that use of DMSO as a solvent for TDI yielded a variety of degradation products, including TDA. NTP (1986) reported that the normal corn oil used in the bioassay had residual moisture of about 0.05%, facilitating reaction of TDI with water and potential formation of TDA. In addition, page 60 of this Toxicological Profile notes that after oral exposure, TDI is hydrolyzed in the gastrointestinal tract to TDA. This is due to the acidic, aqueous environment of the stomach favoring formation of TDA rather than further reactions with isocyanate groups to form polyureas. It should be noted that the identity of the reaction products after degradation of TDI in the corn oil vehicle were not identified by NTP (1986). It should be added that in a peer-reviewed publication, Sielken et al. (2012) reported that the tumors observed after oral gavage exposure to TDI are consistent with the conversion of a small fraction (approximately 5%) of the administered TDI dose to TDA. The dosing solutions may have contained at least 1% TDA, and this conversion to TDA was further augmented by administering the test samples into the acidic environment of the stomach. Thus, similar to how page 97 of this Toxicological Profile notes that it has been suggested that TDA is responsible for positive mutagenicity tests of TDI, a similar statement should be made regarding the suggestion that TDA is responsible for the tumor formation in the oral gavage bioassay"

RESPONSE 18: *A discussion was added that the tumors were the same as observed in rats and mice exposed to 2,4-diaminotoluene and that the carcinogenicity of TDI could be attributed to metabolites similar to those of TDA.*

COMMENT 19 (Section 3.3): The Reviewer notes **"**The discussion of *in vivo* genotoxicity in humans (page 56, lines 1-15) leaves out important study limitations. Both Bilban et al. (2004) and Marczynski et al. (2005) did not adjust for smoking in their analyses and did not acknowledge other known or potential exposures in the workplace besides TDI. An additional study is missing: Holmen et al. (1988) reported no increases in chromosome aberrations, sister chromatid exchanges, or micronuclei in peripheral blood lymphocytes of workers exposed to TDI at a concentration range exceeding that in the study by Bilban et al. (2004) by an order of magnitude."

RESPONSE 19: *A statement was added that the Bilban et al. (2004) study did not adjust for the significant differences in age and smoking index between the exposed and unexposed groups. Although Marczynski et al. (2005) did not adjust for smoking, it is noted that the percentage of smokers was similar in the three groups. The Holmen et al. (1988) paper was added to Section 3.3.*

COMMENT 20 (Section 3.4): The Reviewer commented **"**There appears to be adequate discussion of absorption, distribution, metabolism and excretion. A general comment about the organization of this section is that it seems redundant and hard to follow. This is because the introductory sections (3.4.1 Absorption, 3.4.2 Distribution, 3.4.3 Metabolism, and 3.4.4 Elimination and Excretion) have a lot of the same information as the sub-sections by exposure route. For example, Sections 3.4.3.1 and 3.4.3.2 seem to repeat a lot of the same information as in the introductory Section 3.4.3, but there would be better flow if the information from the introductory Section 3.4.3 was incorporated into the appropriate places in Sections 3.4.3.1 and 3.4.3.2 and streamlined to reduce redundancy."

RESPONSE 20: *The introductory text in Section 3.4.1, 3.4.2, and 3.4.3 were deleted. The introduction to Section 3.4.3 was left unchanged because it discusses route-specific differences in the metabolism of TDI.*

COMMENT 21 (page 60, lines 30-31)**:** The Reviewer noted that the text "should indicate that little to no TDI is hydrolyzed to TDA after inhalation exposure."

RESPONSE 21: *The suggested revision was made.*

COMMENT 22 (page 61, lines 5-6): The Reviewer noted " It should be stated here, up front, that TDI in biological samples is hydrolyzed to form TDA for analysis (as it is stated on page 133, line 20), not that TDI is necessarily metabolized to TDA *in vivo* and then the TDA is measured in the urine, blood, etc. Elaborating on the fact that isocyanates in blood and urine exists as one or more conjugates, so nearly all methods used to quantify TDI or MDI in biological samples require an initial chemical hydrolysis step to cleave the conjugated product to the free amine compound, would be helpful for the reader to understand this."

RESPONSE 22: *In response to COMMENT 20, the referenced text was deleted from the profile.*

COMMENT 23 (page 66, line 17): The Reviewer commented ""isocyanato moiety was capable being" should be "isocyanate moiety was capable of being."

RESPONSE 23: *The suggested revision was made.*

COMMENT 24 (page 68, line 25): The Reviewer commented "should indicate that little to no TDI is hydrolyzed to TDA after inhalation exposure."

RESPONSE 24: *The suggested revision was made.*

COMMENT 25 (page 68, lines 29-31): The Reviewer commented "it is not entirely correct that 10% of metabolites detected by Timchalk *et* al. (1994) after inhalation exposure were "free or acetylated" TDA. Timchalk et al. (1994) clearly state on page 186 of their publication that no free TDA was detected after inhalation. So the 10% is comprised of only acetylated TDA. The correct information appears to be noted later, on page 71 of this Toxicological Profile, in which the Timchalk results for inhalation are repeated."

RESPONSE 25: *The suggested revision was made.*

COMMENT 26 (page 69, Figure 3-4): The Reviewer commented "This figure, adapted from a 1994 publication, presumes that complete hydrolysis of TDI to TDA is required to occur *in vivo* in order for acetylated derivatives of TDA to be present in urine. However, more recent evidence from a study with MDI indicates that it is possible for acetylated MDA conjugates to form *in vivo* without the formation of a free MDA intermediate, and this should be analogous for TDI. The primary literature for this evidence is by Reisser *et al*. (2002) and is discussed in detail on page 395 of the publication by Prueitt *et al*. (2013)."

RESPONSE 26: *Figure 3-4 illustrates a proposed metabolic scheme for 2,4-TDI; it would be speculative to include the Reisser et al. (2002) findings for 4,4'-MDI in this figure.*

COMMENT 27 (Section 3.5): The Reviewer commented "All possible mechanisms of action for the respiratory effects of TDI and MDI are discussed."

RESPONSE 27: *No revisions were suggested.*

COMMENT 28 (page 78, line 19): The Reviewer commented "should indicate that little to no TDI is hydrolyzed to TDA after inhalation exposure."

RESPONSE 28: *The suggested revision was made.*

COMMENT 29 (page 80, line 5): The Reviewer noted ""carbamolylating" should be "carbamoylating""

RESPONSE 29: *The suggested revision was made.*

COMMENT 30 (Sections 3.6 and 3.7): The Reviewer noted "These sections seem appropriate given the limited data. On page 83, lines 13-14, should this sentence be in bold font? It seems like it should not be in bold font, similar to the sentence below it on line 16."

RESPONSE 30: *The text should not be bolded and has been corrected.*

COMMENT 31 (Section 3.8): The Reviewer noted "The biomarkers of exposure and effect and their specificity are adequately described."

RESPONSE 31: *No revisions were suggested.*

COMMENT 32 (page 87): The Reviewer noted "it bears repeating at the beginning of this section that TDI and MDI in biological samples are hydrolyzed to form TDA and MDA for analysis, and it is not necessarily that TDA and MDA form *in vivo* and are then measured as biomarkers. Although the second sentence mentions TDA has been measured in hydrolyzed urine, it is not entirely clear to the reader that the TDA is formed from TDI in the urine as a result of this hydrolysis."

RESPONSE 32: *A statement was added that the TDA was likely released by hydrolysis of protein adducts.*

COMMENT 33 (Section 3.10): The Reviewer noted "The discussion of populations that are unusually susceptible is adequate."

RESPONSE 33: *No revisions were suggested.*

COMMENT 34 (Section 3.11): The Reviewer noted "The methods for reducing toxic effects by use of asthma medication appear to be well-accepted treatments. They do not prevent the substance from reaching the target organ."

RESPONSE 34: *No revisions were suggested.*

COMMENT 35 (Section 3.12): The Reviewer noted "The data needs are presented without apparent bias, and the data needs appear to be adequate and well-described."

RESPONSE 35: *No revisions were suggested.*

COMMENT 36 (Figure 3.6) : The Reviewer noted "Figure 3-6 should have a dot for human genotoxic effects *via* inhalation exposure, as the studies by Bilban (2004) and Marczynski et al. (2005), discussed in Section 3.3, as well as a study by Holmen et al. (1988) that I have noted in my comments above for Section 3.3, fill this data gap."

RESPONSE 36: *The suggested revision was made.*

COMMENT 37 (page 97, line 21): The Reviewer noted "should read "The available data on the reproductive toxicity of TDI consists of…""

RESPONSE 37: *The suggested revision was made.*

COMMENT 38 (page 99, lines 28-29): The Reviewer noted "should indicate that little to no TDI is hydrolyzed to TDA after inhalation exposure."

RESPONSE 38: *The suggested revision was made.*

COMMENT 39 (Chapter 4): The Reviewer stated "I am not aware of any information that is wrong or missing in this section."

RESPONSE 39: *No revisions were suggested.*

COMMENT 40 (Chapter 5): The Reviewer stated "I am not aware of any information that is wrong or missing in this section."

RESPONSE 40: *No revisions were suggested.*

COMMENT 41 (Chapter 6): The stated "The text appears to appropriately trace the substances from their point of release to receptors and to provide sufficient information regarding occurrence at NPL sites. The text also adequately covers information relative to transport, partitioning, transformation, and degradation of the substance in all media. The discussion of levels in the environment is adequate as well, as are the discussions regarding general population and occupational exposure and populations with potentially high exposures." The Reviewer also stated "The data needs are presented without apparent bias, and they appear to be adequate and well-described."

RESPONSE 41: *No revisions were suggested.*

COMMENT 42 (page 130, line 16): The Reviewer noted "the statement that TDI and MDI are mutagenic compounds is a bit strong, given the discussion in Section 3 regarding the likelihood that positive mutagenic effects of TDI *in vitro* were due to the formation of TDA, and the fact that the animal in vivo genotoxicity data are negative and the human *in vivo* genotoxicity data are limited by a lack of accounting for other exposures and smoking."

RESPONSE 42: *The text was revised to remove the statement that TDI and MDI are mutagenic to be consistent with data from Section 3.*

COMMENT 43 (page 131, line 23): The Reviewer identified a typographical error, the word "predominately" needs to be changed with the word "predominantly".

RESPONSE 43: *The revision was made as suggested.*

COMMENT 44 (page 138, line 8): The Reviewer identified a typographical error, the phrase "In study" needs to be changed to "In a study".

RESPONSE 44: *The revision was made as suggested.*

COMMENT 45 (page 138, lines 5-10 and 33-34 and page 139, lines 1-4): The Reviewer questioned if these paragraphs should be in non-bold font.

RESPONSE 45: *The referenced text is part of ATSDR boilerplate; the bolding is removed for the final version of the profile.*

COMMENT 46 (Chapter 7): The Reviewer stated "I am not aware of additional methods, and the methods for measuring key metabolites were previously mentioned in the text, briefly."

RESPONSE 46: *No revisions were suggested.*

COMMENT 47 (Table 8-1): The Reviewer noted "I am not aware of other appropriate regulations or guidelines."

RESPONSE 47: *No revisions were suggested.*

Comments provided by Peer Reviewer #2:

COMMENT 1: The Reviewer noted ""Methylenediphenyl diisocyanate" is sometimes written as "Methylene diphenyl diisocyanate." For consistency, it should always be written "Methylenediphenyl diisocyanate" as in the title of the document. "

RESPONSE 1: *The suggested revision was made.*

COMMENT 2: The Reviewer noted "For consistency, "4,4-Methlyenediphenyl diisocyanate" and "4,4-MDI" should be written as "4,4'-…" everywhere. Searching shows some written each way."

RESPONSE 2: *The suggested revision was made.*

COMMENT 3 (page 15): The Reviewer noted "This outlines a calculation of a "human equivalent concentration (HEC)" but the LOAEL is already referring to humans. It could be referred to instead as an "adjusted NOEL ($NOEL_{ADJ}$)" since it is adjusted to 24-hour exposure, or simply just say that the NOEL was adjusted."

RESPONSE 3: *The text was revised to indicate the LOAEL adjusted to continuous 24-hour exposure is a* $LOAEL_{ADJ}$.

COMMENT 4 (page 18, second sentence under Chronic Duration): The Reviewer commented "The bronchopneumonia was observed in male and female rats, although the species is not mentioned here."

RESPONSE 4: *The suggested revision was made.*

COMMENT 5 (page 23, lines 16-18): The Reviewer noted "Figure 3-x referred to here is not present, so if the figure is not to be developed then remove the discussion of it."

RESPONSE 5: *The suggested revision was made.*

COMMENT 6 (page 31, lines 29-30): The Reviewer commented "Please clarify this sentence. It may be Monday to the following Monday, or Monday morning to Friday afternoon."

RESPONSE 6: *The text was corrected to indicate Monday afternoon values were compared to Monday morning values.*

COMMENT 7 (page 31, line 24): The Reviewer commented "Cumulative and highest-to-date exposures are normally different measures. Authors please check if this edit represents your meaning."

RESPONSE 7: *One of the exposure metrics used by the investigators was "cumulative highest-to-date"; the paper did not provide a definition of this term. A note was added to the profile indicating that the investigators did not provide information on how the exposure metrics were calculated.*

COMMENT 8 (page 42, lines 27-30): The Reviewer noted "These SMRs are not reported in Table 3-4. Please add if possible. "

RESPONSE 8: *Schnorr et al. (1996) did not provide sex-specific SMRs for Non-Hodgkin's lymphoma and Hodgkin's disease.*

COMMENT 9 (page 47, lines 8-9): The Reviewer commented "This statement (No neoplastic lesions…) is contrary to effects noted in section 3.2.2.7 referring to neoplasms in the liver. "

RESPONSE 9: *The text was corrected to indicate no non-neoplastic lesions were observed in the liver.*

COMMENT 10 (page 61, beginning on line 14): The Reviewer commented "Absorption of inhaled TDI is estimated here based on urinary TDA. This is not a useful means of estimation given that little inhaled TDI is expected to be transformed to TDA, as noted on the previous page and several other places. The reporting that follows (here and in section 3.4.1.1) of the fraction converted to urinary TDA is useful, but its importance in determining the overall absorption of TDI should not be overstated."

RESPONSE 10: *The discussion in question was deleted from the profile.*

COMMENT 11 (page 67, Table 3-10): The Reviewer commented "The totals in this table do not appear to be correct. Please check them."

RESPONSE 11: *The values in Table 3-10 are consistent with the values reported in the Gledhill et al. (2005) paper. We do note that the values for the individual tissues at 168 hours post-exposure exceeds the reported total.*

COMMENT 12 (page 75, lines 8-10): The Reviewer noted "It says here that the maximum concentrations were reached in the first 12 hours for both compounds and "Regardless of applied concentration." But note that the Tmax is listed as 87 hours in the 1% 2,6-TDA column of Table 3-12)."

RESPONSE 12: *Table 3-12 was corrected to indicate that the Tmax for 1% 2,6-TDA was 12 hours.*

COMMENT 13 (page 76): The Reviewer commented "Tmax of 87 hours listed for 1% TDA. Please check, as per previous comment.

RESPONSE 13: *The table has been corrected (see RESPONSE to previous comment).*

COMMENT 14 (pages 75, 77-79): The Reviewer noted "Section 3.4.5 and the accompanying Figure 3.5 are a very good introduction to PBPK and PD modeling for chemicals that have them, but a short statement would be adequate for this section since no such models were found, referenced, or used in this report. In particular, note the statement near the end of this section: "If PBPK models for toluene diisocyanates and methylenediphenyl diisocyanates exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations." This reads as though the authors don't know if there are such models or not, and if so promise to use them in various places, but the next sentence summarizes that there are no PBPK or

PD models, so this is not appropriate. (I realize this is a result of starting with a general outline, but this document is being written for specific chemicals.)"

RESPONSE 14: *The text was revised and the statement in question was deleted.*

COMMENT 15 (pages 82-83): The Reviewer noted "Since no relevant studies were found, consider shortening this introductory discussion of neuroendocrine toxicity and the "endocrine disruptor" controversy."

RESPONSE 15: *The text was revised to shorten the introduction to the neuroendocrine toxicity section.*

COMMENT 16 (page 94, Figure 3-6): The Reviewer commented "Based e.g. on the discussion of work by Bilban et al. (2004) (p. 97, 1st para under Genotoxicity), consider adding a circle for human, inhalation, under Genotoxic."

RESPONSE 16: *The figure has been corrected.*

COMMENT 17 (page 154, Table 8-1): The Reviewer commented "Several items in the table say "No data." Where there is a well-defined list (e.g. National primary drinking water standards) that has been checked and TDI and MDI are not present, then it would be more appropriate to say "Not listed" or "Not applicable." Otherwise the reader will not know if the standard or category applies."

RESPONSE 17: *Table 8-1 was revised to change "no data" to "not listed."*

COMMENT 18 (page 25, line 19): The Reviewer requested adding the TDI concentration for the challenge test in the Saetta et al. (1995) study.

RESPONSE 18: *The TDI challenge dose of 5–6 ppb was added.*

COMMENT 19 (Table 3-3): The Reviewer suggested two revisions to the table: Clark et al. (1998) examined workers at 12 polyurethane foam manufacturing facilities and editorial revisions to the study description of the Clark et al. (2003) study.

RESPONSE 19: *The suggested revisions were made.*

COMMENT 20 (Table 3-8): The Reviewer noted that the text for the Ji et al. (2008) study states that a positive response was found for chromosomal aberrations but the table states it was for micronuclei.

RESPONSE 20: *The study found increases in chromosomal aberrations; the table was corrected.*

COMMENT 21 (Section 3.3): The Reviewer noted that the results of the Marczynski et al. (2005) MDI tests were listed in Table 3-8 but was not discussed in the text.

RESPONSE 21: *A discussion of the MDI results were added to the text.*

COMMENT 22 (Table 3-8): The Reviewer noted that the Vock and Lutz (1997) and Vock et al. (1995) studies were not listed in Table 3-8.

RESPONSE 22: *The results of the studies were added to Table 3-8.*

COMMENT 23 (Section 3.4.1.1): The Reviewer noted that no reference was provided for the rat study examining the absorption of MDI**.**

RESPONSE 23: *The citation (Gledhill et al. 2005) was added to the text.*

COMMENT 24 (Table 3-12): The Reviewer noted that the T_{max} for 2,6-TDA was listed as 87 in Table 3-12 and as 12 in the text.

RESPONSE 24: *The value in the table was revised to 12.*

COMMENT 25 (page 93, line 34): The Reviewer noted that the polymorphism is for catenin alpha 3, not the reported catenin alpha 2.

RESPONSE 25: *The suggested revision was made.*

COMMENT 26 (Table 4-2): The Reviewer suggested that the conversion factor for 2,6-TDI was incorrect.

RESPONSE 26: *The conversion factor was corrected to 1 mg/m^3=0.14 ppm.*

COMMENT27 (page 115, last paragraph in Section 5.2): The Reviewer noted that export data for TDI was discussed in the previous paragraph.

RESPONSE 27: *The sentence was corrected to note that no export data were located for MDI.*

COMMENT 28 (page 133, lines 4-6): The Reviewer commented "some context, e.g., what was coated or area or amount applied, would make these amounts more useful."

RESPONSE 28: *The water sealant was applied to concrete; this information was added to the profile.*

COMMENT 29 (page 133, lines 27-29): The Reviewer commented "These are the same values presented in the previous section, 6.4.4, but there it says "within one hour." Was the emission complete within 30 minutes? Is one or the other in error? Please check."

RESPONSE 29: *The text in Sections 6.4.4 and 6.5 were revised to clarify that emission data were reported for 30 minutes at 21°C and 1 hour at 27°C.*

COMMENT 30 (page 153, line 5): The Reviewer noted that the $BMCL_{HEC}$ should be 0.062 mg/m^3

RESPONSE 30: *The value was corrected to 0.06 mg/m^3, as reported on IRIS.*

COMMENT 31 (page 153, line 6): The Reviewer corrected "intraindividual" to "interindividual"

RESPONSE 31: *EPA refers to this uncertainty as "10 for intraindividual variation;" thus, no changes were made to the profile.*

COMMENT 32: The Reviewer suggested a number of editorial revisions to the toxicological profile

RESPONSE: *The suggested revisions were made.*

Comments provided by Peer Reviewer #3:

COMMENT 1 (page 1; TDI and MDI at hazardous waste site): The Reviewer commented "This conclusion concentrates on the negative without giving appropriate recognition to the fact that neither TDI nor MDI is naturally occurring or has it been found widely in hazardous waste sites as such in infers a greater risk than is likely to be the case."

RESPONSE 1: *This statement is alerting the reader to the fact that TDI and MDI may not have been measured at all NPL sites and that additional site monitoring may result in the identification of more sites with these compounds.*

COMMENT 2 (page 2, How are TDI and MDI used?): The Reviewer commented "The use of the term "combine" does not adequately reflect the fact that MDI and TDI are polymerized in the final product that consumers are typically exposed to."

RESPONSE 2: *Although the term "combine" may not adequately describe polymerization, ATSDR believes that it is a more understandable term for the general public.*

COMMENT 3 (page 2, Where are TDI and MDI found?): The Reviewer commented "May also be due to the low levels of release? I have not had time to extensively interrogate the TRI release data but the few that I did look at do not report releases so this may be a reasonable conclusion."

RESPONSE 3: *In tests conducted by Kelly et al. (1994), the levels of TDI emitted from a number of consumer products were below the detection limit.*

COMMENT 4 (page 4, TDI and MDI and cancer): The Reviewer suggested adding "but their relevance to humans remains unclear" to the end of the study discussing the NTP (1986) study.

RESPONSE 4: *Adding the statement "but their relevance to humans remains unclear" implies that animal model is not relevant; ATSDR did not identify support for this statement. The oral cancer study may not be relevant to humans because they are unlikely to be exposed to TDI or MDI via oral exposure. In several sections of the revised Public Health Statement, it is stated that oral exposure to TDI or MDI is unlikely.*

COMMENT 5 (page 5, What about birth defects): The Reviewer suggested adding "The relevance of this to humans is unclear" to the end of the sentence.

RESPONSE 5: *The Reviewer did not provide support for their contention that the animal developmental toxicity data are not relevant to humans.*

COMMENT 6 (page 6, TDI and MDI can be measured in blood and urine): The Reviewer commented "I understand that TDI and MDI are hydrolyzed in the body but are not subject to metabolism. I think that the use of the term metabolism conveys the wrong message."

RESPONSE 6: *The text was revised to indicate that TDI, MDI, and their hydrolysis products could be measured in blood and urine.*

COMMENT 7 (page 7): The Reviewer commented "I intend not to correct these throughout the rest of the document. I think that the authors need to be consistent. When referring to TDI and MDI as chemicals the plural should not be used i.e. toluene diisocyanate and methylenediphenyl diisocyanate. The plural should be used when referring to diisocyanates"

RESPONSE 7: *The suggested revision was made.*

COMMENT 8 (page 9, second paragraph): The Reviewer commented "As a general rule I would prefer to cite original source not a secondary source."

RESPONSE 8: *As a general rule, ATSDR relies on primary sources; however, secondary sources are acceptable for reporting physical and chemical properties data.*

COMMENT 9 (page 9, third paragraph): The Reviewer commented "As I understand it TDI is not a gas but can be found as a vapor. MDI is also not found as a gas, but as a condensation aerosol."

RESPONSE 9: *The text was corrected to indicate that exposure to TDI can occur by inhalation of aerosols and vapor and to MDI via exposure to aerosols.*

COMMENT 10 (page 9, fourth paragraph): The Reviewer commented "This is a very important statement and if true needs to be supported by a reliable citation. Is there evidence from the Consumer Products Database or from commercial data? It is not sufficient to cite an example. Overall I'm not convinced by the way this logic is being presented. It appears that there is a fact (measurement of low levels of amines in consumers) which is tenuously being linked to an unsubstantiated claim of increased exposure. "

RESPONSE 10: *This paragraph has been revised. Exposure to TDI resulting from the use of consumer products containing uncured TDI was supported by the results of the Kelly et al. (1999) study, which reported TDI emissions following the application of a concrete water sealant product. Additionally, EPA 2011b was added as a citation for the statement that there is an increase in the use of consumer products containing uncured TDI and/or MDI.*

COMMENT 11 (page 10, first full sentence): The Reviewer commented "I understand that these products only contain MDI. Can this be verified?"

RESPONSE 11: *As noted in the RESPONSE to COMMENT 10, the text in this paragraph has been revised and the referenced statement has been deleted.*

COMMENT 12 (page 10, second sentence): The Reviewer commented "Again, a point of semantics, but the amines are generated after treatment of the biological matrix with acid/base to release the amine from the protein for analytical measurement. Free amines and/or free diisocyanates are not found in biological samples. The amines are not metabolic products"

RESPONSE 12: *The referenced sentence was deleted from the profile in response to COMMENT 10.*

COMMENT 12 (page 12, regarding the NTP 1986 study): The Reviewer commented "These studies have been criticized in several publications."

RESPONSE 12: *The Reviewer did not provide support for this statement.*

COMMENT 13 (page 15): Regarding the acute-duration inhalation MRL, the Reviewer noted "The primary adverse effect from TDI exposure is sensitization. The paragraph before clearly states that acute MRLs may not be protective for health effects–like respiratory allergy–and if this is the primary adverse health effect, then perhaps an acute MRL shouldn't be set at all. If, however, the wish is to set an acute MRL then it is essential to establish that the POD is a NOAEL for asthma. In this regard the paper of Ott et al 2003 is perhaps key. Once this is established Vandenplas is the appropriate study to use as the POD for local acute effects."

RESPONSE 13: *The induction of TDI sensitization, which could result in asthma symptoms, is not likely to be the primary health effect of concern for the general population. Although the exposure scenario which could result in sensitization has not been fully elucidated, it is likely to occur in susceptible subpopulations exposed to very high levels of TDI or from chronic exposure to high concentrations. Once an individual is sensitized, exposure to extremely low levels of TDI could elicit a response; thus, the MRL may not be protective for these individuals. For the general population, acute exposure to TDI is most likely to result in decreases in lung function and this effect was selected as the basis of the acute-duration inhalation MRL.*

COMMENT 14 (page 15): Regarding the uncertainty factor for the acute MRL, the Reviewer commented "This should be more than sufficient for what is effectively a threshold effect."

RESPONSE 14: *No revision was suggested.*

COMMENT 15 (page 16): Regarding the first sentence of the Chronic-Duration MRL section, the Reviewer commented "Several? I would not regard the number of available studies as large but accept that this is a matter of opinion."

RESPONSE 15: *The text was revised to indicate that a number of studies examined TDI workers.*

COMMENT 16 (page 16, last line): The Reviewer commented "I do not understand this. If these individuals were not TDI responders what is the basis for concluding that the effects were indicative of TDI sensitization?"

RESPONSE 16: *The workers did not respond to the low concentration of TDI used in the challenge test; a larger TDI concentration may be necessary to elicit a response.*

COMMENT 17 (page 17): Regarding the statement that TDI sensitization is believed to occur in less than 10% of workers, the Reviewer commented "What is the reference for this belief? I could not find 10% referenced in the Ott paper, they quote 5 to 6% In fact this relates to a 5.6% estimate that comes

from a British study covering the years 1961-1972 (Adams, 1975). Adams WGF. Long-term effects on the health of men engaged in the manufacture of tolylene di-isocyanate. Brit J Ind Med. 32:72-78, 1975."

RESPONSE 17: *The 5–6% reported in the Ott paper and 5.6% reported in the Adams (1975) paper is consistent with the statement that it is found in <10% of workers.*

COMMENT 18 (page 17): Regarding the statement that the primary effect in non-sensitized workers is a decline in lung function, the Reviewer commented "I concur that this is the lead health effect upon which the MRL should be set. However, it is extremely important that not only is the causal relationship between a decline in LF and exposure established, but also the confidence in the NOAEL/LOAEL that will subsequently be used. This strong opening statement belies the inconsistency in the available data and the likelihood that the transient decline in lung function observed by Diem and Clark was not a result of some form of previously undocumented sensitivity, but rather the result of operational circumstances at the two facilities i.e. a new start up facility with greater opportunity for peak exposures during the start up period in the case of Diem, and a change in the law in the UK precluding peak exposures in the workplace in the case of Clark. I recognize that this interpretation requires a broader interpretation than is perhaps typical but the alternative is to base the MRL on a POD for which there is no physiological explanation that I am aware of."

RESPONSE 18: *The first sentence of the paragraph was revised to indicate that the available data suggest that the primary health effect in non-sensitized workers in a decline in lung function. Regarding the comments on the Diem et al. (1982) and Clark et al. (1998), please see the RESPONSES to COMMENTS 19–21. ATSDR disagrees with the Reviewer that the MRL is based on POD for which there is no physiological explanation. Several occupational studies have reported decreases in lung function in TDI workers (Clark et al. 1998; Diem et al. 1982; Huang et al. 1991a, 1991b; Omae et al. 1992; Peters et al. 1968, 1970; Wegman et al. 1977, 1982; White et al. 1980). As with many occupational exposure studies, there is a degree of uncertainty associated with the exposure metrics reported in the Diem et al. (1982) and Clark et al. (1998) studies.*

COMMENT 19 (page 17): Regarding the discussion of the Diem et al. (1982) study, the Reviewer commented "It is important to note here that this was the start of production in a new TDI manufacturing plant in Louisiana. During the start-up of any new plant there are more frequent tasks requiring operator intervention with a greater likelihood of exposure to higher than normal levels of TDI (peak exposures) that would not be reflected in the TWA data presented (only TWA data presented). The significance of this is illustrated in comments provided by Dr G Ott to the ACGIH TLV committee in 2006 on the Draft TLV Documentation for TDI (10/08/2005 Revision) in which he regaled his experience of exposure conditions in TDI facilities in the years leading up to 2000. He describes a history of high exposure to TDI and other chemicals, including phosgene, in this industry. He explained that TDI exposures both TWA and peak, associated with tasks such as line breaking and pump repair that could directly irritate the respiratory tract causing a toxic bronchitis were common place. He linked this with 68% of removals (workers changing work area) due to symptoms occurred within one year of hire into the facility with a large percentage of the cases (38%) developing symptoms within 1 month of assignment to the unit. He explained that the number of cases fell from the mid 60's when the percent of samples exceeding 0.02 ppm dropped, but that TDI concentrations continued to exceed 0.02 ppm well into the 70's when 62% of workers were still being removed due to symptoms in the first year of work in the unit. He went on the explain that the lower TWA exposures routinely reported as being associated with the lower annual incidence rate for asthma of 0.7% also failed to mention that short-term TDI concentrations above 0.02 ppm were routinely observed and that prior acute phosgene or TDI exposure incidents were reported in 6 of the 8 cases identified between 1980 and 1996 (Ott et al., 2000). These findings are similar to those

of Weill et al. (1981), where of 6 of 12 cases had been linked to prior acute overexposure incidents. In the latter study, 50% of the time when routine short-term TDI concentrations exceeded 0.02 ppm they also exceeded 0.04 ppm. On this basis it is equally likely that the greatest declines in lung function occurring during the first several years of exposure to TDI reported by Diem et al. (1982) was due to short-term high level exposure to TDI (that were not reflected in the TWA measurements reported) and that the normal declines in LF observed thereafter reflected steady state plant operation."

RESPONSE 19: *Based on the data provided in the Diem et al. (1982) paper, a determination cannot be made whether the declines in lung function were associated with peak exposure levels occurring during the initial start-up of the facility or were the result of approximately 5 years of exposure to TDI. Cumulative exposure was one of the exposure metrics used in the study, which would be reflective of exposure occurring during the facility start-up. The study did analyze changes in lung function related to peak exposures exceeding 20 ppb and found similar results as for cumulative exposure.*

COMMENT 20 (page 17): Regarding the Clark et al. (1998) study, the Reviewer commented "Mean TDI exposures were assessed by 2294 personal monitoring measurements. 4.7% and 19.0% resp. of the samples taken exceeded the UK 8-h (5.8 ppb) and 15-min (typically set at 3 x TWA) maximum exposure limits for TDI. In 1977 a recommended an inhalation exposure limit of 0.05 mg/m3 (8-hr TWA) was set in the UK. In 1985 this was revised to an 8hr TWA control limit of 0.005"

RESPONSE 20: *Appendix A provides a more in-depth discussion of the Clark et al. (1998) study and notes that 4.7% of the 8-hour TWA concentrations exceeded the 0.0058 ppm limit and 19% of the samples exceeded the 15-minute short term limit of 0.02 ppm.*

COMMENT 21 (page 17): Regarding the discussion of the Clark et al. (1998) study, the Reviewer commented "This comes across as selective reporting from this study abstract focusing on the "small excess" rather than the overall conclusion of the authors that the study did not show a causal relationship. This reinforces the need to explain more transparently the justification for taking the transient effect over the overall effect."

RESPONSE 21: *The text was revised to note that no significant alterations in lung function were observed in the full cohort.*

COMMENT 22 (page 18): Regarding the statement that the declines in lung function in TDI workers occurred at concentrations lower than effects in mice, the Reviewer commented "This is only the case if you assume that the transient increased decline in LF is real and causally related to the TWA TDI levels cited. If the findings of the longer duration studies are given greater significance then the adverse effect levels in animals and humans is more comparable."

RESPONSE 22: *ATSDR believes that the decline in lung function is a well-supported finding. Clark et al. (1998) suggested that the decreased lung function observed in the naïve workers was due to respiratory irritation. It is likely that the workers developed a tolerance to the irritating effects of TDI; thus, the decline in lung function was only observed when the workers began working at the facility. There is some degree of uncertainty associated with the TWA TDI levels and it is not known if the effects resulted from the peak exposure levels. However, there is greater confidence in deriving an MRL from the human data than the animal data, especially since the chronic-duration animal studies did not evaluate lung function.*

COMMENT 23 (page 18): Regarding the consideration of using the Clark et al. (1998) and Diem et al. (1982) studies as the basis of the chronic MRL, the Reviewer commented "The greatest declines in lung function occurring during the first several years of exposure to TDI reported by Diem et al. (1982) and Clark et al. (1998) could be due to short-term high level exposure to TDI and/or exposure to other toxic chemicals. Furthermore in the absence of a recognized mechanism by which these transient effects could be caused this alternative explanation seems most likely. In terms of alternative PODs upon which to base the chronic MRL there are 3 potential options; 1) use the epidemiological studies post 2000 which tend to support a NOAEL around 5ppb. 2) base the MRL on the animal data which is more consistent. 3) a combination of both using a weight of evidence approach. I would suggest option 3 is consistent with contemporary guidance and expectations and would lead to a more robust proposal.

RESPONSE 23: *ATSDR believes that the weight of evidence supports the identification of declines in lung function as a critical effect of TDI exposure based on the consistency of the finding in at least 10 occupational exposure studies. Clark et al. (1998) suggested that the decline in lung function observed during the first several years of exposure may be the result of respiratory irritation. Continuous exposure to TDI may result in development of a tolerance to the irritation. The Reviewer suggested three alternative approaches for derivation of an MRL for TDI. The first was to base the MRL on post-2000 studies. ATSDR only identified one post-2000 study (Ott et al. 2000). This longitudinal study examined workers employed between 1967 and 1992 and reported no alterations in lung function in workers with a TWA TDI exposure level of 0.0042 ppm. As with other occupational exposure studies, peak exposures exceeded 20 ppb (levels of 60–80 ppb were reported for some job categories). Thus, there is some degree of uncertainty associated with the exposure metric for the Ott et al. (2000) study. The animal studies were not considered a suitable basis for the MRL because they did not examine lung function; the lowest LOAELs were identified for histological damage in the nasal cavity. The third approach suggested by the Reviewer was a weight-of-evidence approach, which combines the first two approaches. ATSDR used a weight-of-evidence approach to identify the critical target and used the animal data as support for identifying the respiratory tract as a sensitive target.*

COMMENT 24 (page 18): Regarding the selection of Clark et al. 1998) over Diem et al. (1982) as the basis of the MRL, the Reviewer commented "I am not sure that this is a valid reason for deselection since Diem included extensive monitoring data in his publication: l,949 8-h, TWA measurements that ranged from a minimum of 0.l ppb to a maximum of 25 ppb. Twenty-fifth, fiftieth, and seventy-fifth percentiles were 1.1, 2.0, and 3.5 ppb, respectively. The geometric mean was 2.00 ppb and the geometric standard deviation was 2.94 ppb."

RESPONSE 24: *The most sensitive effect observed in the Diem et al. (1982) was the decrease in lung function in workers who never smoked; the published paper did not report exposure data for this group. EPA used unpublished data to calculate the LOAEL; these data were not available to ATSDR. Rather than cite the exposure metric to a secondary source, ATSDR chose to base the MRL on the Clark et al. (1998) study, which identified a similar LOAEL value.*

COMMENT 25 (page 18): Regarding the derivation of the chronic MRL, the Reviewer noted "I support this extrapolation from the POD but believe that the basis for the POD is flawed."

RESPONSE 25: *See the RESPONSES to COMMENTS 20–24.*

COMMENT 26 (page 18): Regarding derivation of an oral MRL for TDI, the Reviewer commented "Previously it was stated on page 25 that this was an unlikely route of consumer exposure since it was not present in food or drinking water. Is it perhaps not appropriate therefore to conclude that oral MRLs are not required rather than giving the impression that the data are inadequate to generate an acute or intermediate MRL?"

RESPONSE 26: *The text was revised to indicate that TDI is rapidly hydrolyzed in water and is not detected in aquatic environments; thus, oral exposure to humans is unlikely and oral MRLs for TDI are not needed.*

COMMENT 27 (page 20): Regarding the statement "the study identified a NOAEL of 0.2 mg/m^3", the Reviewer commented "I believe that this refers to the paper by Feron et al., Chronic pulmonary effects of respirable methylene diphenyl diisocyanate (MDI) aerosol in rats: combination of findings from two bioassays. Arch. Toxicol., Vol.75, (3), May, 2001, 159-75 It was concluded that the results of the two studies could be combined to serve as a basis for human risk assessment of MDI. If this is a valid conclusion this should be considered as an alternative POD since for inflammatory and other non-neoplastic pulmonary changes, the lowest dose examined (559 mg/m3) was regarded as a NOEC for both polymeric and monomeric MDI. Two independent bioassays are available which have examined the potential carcinogenicity of monomeric and polymeric methylene diphenyl diisocyanate (MDI) following long-term inhalation exposure in rats. These studies are not directly comparable, however, due to differences in design and conduct of the in-life phase, and differences in nomenclature used for some of the histopathological findings. This paper presents a definitive overview of the pulmonary toxicity of MDI developed following a thorough review of both investigations. As part of this process, the test materials and the designs of the studies were compared, and an in-depth review of lung lesions was conducted by an independent reviewing pathologist. This included the re-examination of the original lung slides, supported by an analysis of the exposure regimens, the results of which were used to develop an accurate profile of the doses received by the animals in the two studies. Histopathological findings were then combined with this information to give an overall dose-response curve for both studies as a whole. The range of total inhalation exposures to MDI was calculated as 559, 1972, 2881, 6001, 17,575 and 17,728 mgh/m3. Major pulmonary effects included increased lung weights together with bronchiolo-alveolar adenomas and hyperplasia, and interstitial fibrosis which occurred consistently in both studies, indicating a very similar qualitative response of the lungs to polymeric and monomeric MDI. The quantitative response of the lung was clearly dose-related in each study, and when the studies were considered as a whole a reasonable overall dose-response relationship was apparent for major lung lesions. Lung tumours (in low incidences) only occurred at the highest dose level in both studies (17,575 and 17,728 mgh/m3).

RESPONSE 27: *The NOAEL of 0.2 mg/m^3 was identified in the Reuzel et al. (1994) study. Feron et al. (2001) concluded that the results of the Reuzel et al. (1994) and an unpublished study by Hoyemann et al. (1998) were consistent and identified a NOAEL of 0.2 mg/mg^3.*

COMMENT 28 (page 20): Regarding the discussion of the chronic inhalation data for MDI, the Reviewer commented "Should not the 17h/day 5 d/w, 2 year study by Hoymann 1985 also be mentioned here?"

RESPONSE 28: *ATSDR was unable to obtain a copy of the unpublished Hoyemann et al. (1998) study; however, a summary of the study (as reported by Feron et al. 2001) was added to the profile.*

COMMENT 29 (page 20): Regarding the selection of the critical study for the MDI MRL, the Reviewer commented "I believe that I have established an alternative interpretation of these findings. As such there is no reason why a WoE approach could not also be taken for MDI i.e. using the Reuzel study as the POD and then remarking on the positive concordance with the findings of Solotto."

RESPONSE 29: *This approach is similar to the one used to derive the MRL.*

COMMENT 30 (page 21): Regarding the oral MRL for MDI, the Reviewer commented "Same comment as for TDI; oral route of exposure does not appear to be relevant."

RESPONSE 30: *A statement was added that oral exposure to MDI is not likely because it is rapidly hydrolyzed in water; thus, oral MRLs for MDI are not needed.*

COMMENT 31 (page 23, line 15): The Reviewer commented "MDI is not a carcinogen."

RESPONSE 31: *The Reuzel et al. (1994) reported a significant increase in lung adenomas at 6 mg/m^3, which was considered a cancer effect level. The identification of a CEL does not necessarily indicate that MDI is a carcinogen.*

COMMENT 32 (page 40, line 20): The Reviewer commented "There appears to be no mention of the recent review by Hughes et al. This is a particularly useful review listing all the relevant literature. Hughes MA; Carson M; Collins MA; Jolly AT; Molenaar DM; Steffens W; Swaen GM. 2014. Does diisocyanate exposure result in neurotoxicity? Clin.Toxicol., Vol. 52, (4), Apr., 2014, 242-57"

RESPONSE 32: *The Hughes et al. (2014) paper was published after the literature search was conducted. ATSDR has reviewed this systematic review and incorporated the findings into Section 3.2.1.4.*

COMMENT 33 (Table 3-4): The Reviewer suggested adding TDI or TDI and MDI to the table.

RESPONSE 33: *The investigators, particularly Sorahan and Nichols (2002), noted that the workers were exposed to "isocyanates" and noted that MDI was used, but it is not known whether it was used at all facilities examined and TDI is likely the predominant diisocyanate used. The text accompanying the table notes that some facilities also used MDI and lists other compounds utilized at the facilities.*

COMMENT 34 (page 44, line 4): The Reviewer commented "Is it perhaps appropriate to mention the recent paper by Prueitt et al? http://www.ncbi.nlm.nih.gov/pubmed/23675773."

RESPONSE 34: *ATSDR does not typically cite review papers in Section 3.2; the Prueitt et al. (2013) paper was reviewed to identify missing references.*

COMMENT 35 (page 44, line 12): The Reviewer commented "Additional references found but not cited:
Hoymann, H.-G., J. Buschmann, and U. Heinrich. 1995. Examinations about the chronic toxicity/carcinogenicity of 4,4'-methylene diphenyl diisocyanate (MDI). Fraunhofer-Institut fur Toxikologie and Aerosolforshung, Hannover, Germany. Report No. 116-06-084.

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

RESPONSE 35: *The data from the Hoyemann study (as cited by Feron et al. 2001) was added to the profile.*

COMMENT 36 (page 45, line 12): The Reviewer requested that the citation be added to this statement.

RESPONSE 36: *The citation (NTP 1986) was added.*

COMMENT 37 (page 48, line 4): The Reviewer commented "Again the Hughes et al 2014 paper appears to be relevant here."

RESPONSE 37: *The Hughes et al. (2014) review of the neurotoxicity of diisocyanates did not discuss oral exposure.*

COMMENT 38 (page 48, line 26): The Reviewer commented "Prueitt et al 2013 should perhaps be included"

RESPONSE 38: *The Prueitt et al. (2013) paper is a review article and was not added to this section of the profile. The text in this section was expanded to include a comment by Dieter et al. (1990) that the observed tumors were similar to those resulting from 2,4-diaminotoluene exposure and could be attributed to the formation of 2,4-diaminotoluene in the gut. This is similar to Prueitt's conclusions.*

COMMENT 39 (page 50, line 22): The Reviewer commented "TDI is not discussed. Is this intentional?"

RESPONSE 39: *As noted in the beginning of Section 3.2.3.2, no information was available regarding systemic effects in humans or animals exposed to TDI.*

COMMENT 40 (page 87, line 5): The Reviewer commented "As mentioned previously this is not a metabolite but a hydrolysis product"

RESPONSE 40: *The suggested revision was made.*

COMMENT 41 (page 90, line 24): The Reviewer commented "Is it not worthwhile mentioning here that asthma is a multi-factorial disease, and is the result of complex interactions between genetic constitution and environmental factors? From clinical studies with asthmatic and non-asthmatic volunteers it is evident that individuals with a history of atopy, non-specific bronchial hyperresponsiveness, or cigarette smoking are not at greater risk of developing asthma after exposure to diisocyanates (Butcher et al., 1993)."

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RESPONSE 41: *A discussion was added of studies comparing atopy, smoking habits, and response to common allergens among workers responding to a TDI challenge and those not reacting to the challenge.*

COMMENT 42 (page 91, line 25): The Reviewer suggested adding the Bernstein Jolly, Amer. J. Ind. Med., Vol.36, 1999, 459-68 citation.

RESPONSE 42: *The Bernstein and Jolly (1999) paper does not provide information on the treatment following TDI or MDI exposure.*

COMMENT 43 (page 98, line 33): The Reviewer stated "However, it is stated previously that the oral route is not a significant route of exposure so the requirement for this data is rather academic."

RESPONSE 43: *The data need for oral toxicity studies was deleted.*

COMMENT 44 (page 99, lines 11-12): The Reviewer commented "The recent review by Hughes et al 2014 would suggest otherwise."

RESPONSE 44: *The Hughes et al. (2014) weight-of-evidence evaluation concluded that the available data on diisocyanates was not adequate to determine whether there was a causal association between the neurological effects reported in some human studies and diisocyanate exposure. ATSDR believes that this evaluation supports the need to further evaluate the neurotoxic potential of TDI and MDI.*

COMMENT 45 (page 100, line 23-24): The Reviewer stated "Is this correct that free TDI and DMI exist to a significant extent within the body rather than hydrolyzing or conjugating? I understand that MDI and TDI complex with proteins like albumin, glutathione, hemoglobin–so yes, they are widely distributed but only in their conjugated form. No study has shown free MDI or TDI."

RESPONSE 45: *The text was revised to indicate that conjugated TDI and MDI are widely distributed.*

COMMENT 46 (page 101, lines 28-29 and line 32: The Reviewer commented "From the data presented it is hard to perceive how communities living near a commercial activity would have significant exposure (low occupational levels and short half life). In regard to direct exposure from use of products containing TDI/MDI; by far the largest proportion of products marketed are polymeric so consumers are not exposed to uncured chemical. There appear to be but a few applications where a consumer may be exposed to uncured MDI, so it would appear that this should be the more pressing focus of any attention. " **and "**Is there really a significant potential for exposure to children that justifies this statement?"

RESPONSE 46: *The profile states that there is a potential for children to be exposed to diisocyanates and there are no data to determine if they would be more sensitive than adults. The purpose of the Data Needs section of the profile is to identify data gaps; this section does not prioritize the data need.*

COMMENT 47 (Table 4-1): The Reviewer stated "Same comment as previous re primary sources. I am surprised that HSBD is used as a primary data source since there are other far more reliable databases such as the ECHA dissemination website."

RESPONSE 47: *As a general rule, ATSDR relies on primary sources; however, secondary sources are acceptable for reporting physical and chemical properties data. The data from HSDB is verified by checking other sources.*

COMMENT 48 (page 108, third paragraph): The Reviewer commented "This is also more appropriately stated under 5.3."

RESPONSE 48: *The referenced sentence was deleted from the profile; similar information is already provided in Section 5.3.*

COMMENT 49 (page 114, second paragraph): The Reviewer stated "My understanding is that TDI is only available to professionals and skilled trades persons. MDI may be used by non-professionals (DIY Market). I suggest that this is clarified before finalizing the review."

RESPONSE 49: *According to EPA (2011b) some products containing uncured TDI are labelled "for professional use;" however, the products could be purchased by consumers or used in the presence of consumers.*

COMMENT 50 (page 116, line 16): The Reviewer commented "As mentioned previously I believe that only MDI based products are sold to the general public."

RESPONSE 50: *See RESPONSE to COMMENT 49.*

COMMENT 51 (page 131, line 15): The Reviewer commented "Creating potent irritants? A clumsy sentence - "TDI and MDI are highly reactive and interact with biological molecules. Inhalation of MDI or TDI can result in respiratory tract irritation"

RESPONSE 51: *The referenced sentence was deleted from the profile.*

COMMENT52 (page 131, line 16): The Reviewer commented "MDI and TDI are not classified as mutagenic."

RESPONSE 52: *The referenced sentence was deleted from the profile.*

COMMENT 53 (page 131, line 29): The Reviewer commented "This is not a primary reference. It refers to another article–the European Chemicals Agency (2008) Data on manufacture, import, export, uses and releases of 4,4'-diaminodiphenylmethane as well as information on potential alternatives to its use. http://echa.europa.eu/documents/10162/13640/tech_rep_mda_en.pdf ; Publications by Arnold et al 2013 should also be included here for TDI, and Hoffmann et al 2010 for MDI."

RESPONSE 53: *The citation was changed to EPA (2011a).*

COMMENT 54 (page 132, line 23): The Reviewer commented "Comments previously made regarding these statements should be carried throughout the document."

RESPONSE 54: *The sentence was revised to indicate that workers could be exposed to TDI and MDI by inhalation of aerosol and vapor (TDI only).*

COMMENT 55 (page 132, lines 28 and 30-32): The Reviewer commented "This is a relatively old study (17yrs). It may be more appropriate to use more recent monitoring data since more restrictive TLVs and modern manufacturing methods have significantly reduced occupational exposure levels." and **"**Again are there not more recent data? Surely IARC data of 30-40 years ago can be improved upon."

RESPONSE 55: *More recent data (Lesage et al. 2007) are discussed at the end of the referenced paragraph.*

COMMENT 56 (page 143, line 1): The Reviewer commented "Amine hydrolysis products not metabolites. MDI and TDI are not metabolized to free amines."

RESPONSE 57: *The text was revised to indicate that amine hydrolysis products could be detected in plasma.*

COMMENT 58 (Table 8-1): Regarding the inclusion of the cancer classification for polymethylene polyphenyl isocyanate, the Reviewer commented "Is the inclusion of this substance significant as is not discussed or described elsewhere in the document?"

RESPONSE 58: *The data for polymethylene polyphenyl isocyanate was deleted from the profile.*

COMMENT 59: The Reviewer suggested a number of editorial revisions to the toxicological profile

RESPONSE: *The suggested revisions were made.*