Disposition of Peer Review Comments for Toxicological Profile for Toluene

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 were:

Luis Haro Garcia, Ph.D.
Departamento de Salud Pública,
Facultad de Medicina,
Universidad Nacional Autónoma de México
México DF, México

Zemin Wang, M.D., Ph.D., DABT
Department of Environmental Health
Indiana University
Bloomington, IN

Scott E. Bowen, Ph.D.
Associate Professor and BCN Area Chair
President, Michigan Chapter of the Society for Neuroscience
WSU Psi Chi Advisor
Department of Psychology
Wayne State University
Detroit, MI

Review comments provided by Reviewer #1:

CHAPTER 1. PUBLIC HEALTH STATEMENT

COMMENT: It seems to me that the information contained in this chapter is adequate for understanding of the average citizen, at least of the United States of America; however, I should not consider myself as the most suitable person for being able to point out that about this chapter; I think is more appropriate to ask someone with experience in education since the intention is that children and adolescent population, and so the elderly, has access to a document of this kind.

RESPONSE: *No revisions were suggested.*

COMMENT: The major headings established as questions seem to me wise; it always call attention to ordinary people who having doubts about technical and complex issues. I do not think the scientific terms require further explanation, though it would be desirable to count with the direct opinion of the general public about the content of the "Profile"."

RESPONSE: *No revisions were suggested.*

COMMENT: "In this very first chapter, I think is necessary to clear what means "short-term" exposure and "long-term" exposure"

RESPONSE: *The terms "short-term" and "long-term" were replaced with "single exposures to toluene or repeated exposures over a few weeks" and "day-after-day exposure to toluene," respectively.*

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

COMMENT: In Section 2.1, the proposed subheading is: **"BACKGROUND AND ENVIRONMENTAL EXPOSURES TO TOLUENE IN THE UNITED STATES"**, but in my opinion could be **"BACKGROUND AND ENVIRONMENTAL SOURCES OF TOLUENE IN THE UNITED STATES ".**

RESPONSE: *The headings in this chapter are standardized headings for ATSDR profiles. ATSDR will consider the suggestion during the next revision of the ATSDR profile format.*

COMMENT: In Section 2.2., seems to be the intention to divide the effects in "Death" and "Systemic effects"; these "Systemics effects" subsection, the human apparatuses or systems affected initiate in the text with italic and bold letters, but from Immunological and Lymphoreticular Effects no longer appear as such, is there any reason for this?

RESPONSE: *The sections in Chapter 2 follow the organization of Chapter 3, which separates specialized systems/effects (Immunological and Lymphoreticular Effects, Neurological Effects, Reproductive Effects, Developmental Effects, and Cancer Effects) from other systemic effects.*

COMMENT: On line 15 on page 17, on **Endocrine effects**, I would request you kindly, to include the findings of Miranda-Figueroa et al [Miranda-Figueroa G, Paz-Román MP, Aguilar-Madrid G, Juárez-Pérez CA, Basurto-Acevedo L, Haro-García L. Male hormonal profile in workers exposed to toluene in

an industrial packaging plant. Rev Med Inst Mex Seguro Soc 2013;51(3):8-11] where is referred that a group of male workers categorized as with high exposure to toluene (level of hippuric acid: 6.31±3.83 g/g creatinine, obtained by Ultra Performance Liquid Chromatography from urine samples), compared with a group categorized as with low exposure to toluene (level of hippuric acid: 2.53±1.20 g/g creatinine with the same method), the serum level of FSH was identified significantly lower (p=0.02), and the LH level also was diminished, but not significantly (p=0.81). Although the serum level of testosterone was unexpectedly on the contrary, the rate anyway was lower than the referred as normal for the general population and by age group.

RESPONSE: *The suggested reference is not available in English. In general, ATSDR only translates a foreign language manuscript if the study appears to be critical to the MRL derivation. Since the critical effect for toluene is neurological effects, translation of this study is not crucial to the derivation of MRLs. Therefore, the ATSDR has decided not to translate this manuscript at this time.*

COMMENT: In addition, among the **Systemics effects**, specifically on the **Neurological Effects (**line 1 of page 21), should be mentioned the ototoxic ones mentioned by Juárez-Pérez et al [Juárez-Pérez CA, Torres-Valenzuela A, Haro-García LC, Borja-Aburto VH, Aguilar-Madrid G. Ototoxicity effects of low exposure to solvent mixture among paint manufacturing workers, International Journal of Audiology 2014;53:370-376] who in workers exposed to low concentrations of toluene vapors in a paint factory (TWA median: 13.4 mg/m^3) and low noise levels that not exceeded the 85dBA (The minimum and maximum noise level in the company were 59.89 to 84.88 dBA measured in 14 work areas), in 9% of them hearing loss was identified. The study revealed the need for more comprehensive assessments that must include BAEP (brainstem auditory-evoked potentials) analysis and the measure of otoacoustic emissions. The workers studied also were exposed to at least 14 more solvents. None of these the TWA was found above the norm.

RESPONSE: *The provided reference was reviewed and added to Section 3.2.1.4, Neurological Effects - Occupational Exposure (pp.72-73). Because of the 14 solvents that could contribute to the observed effects, this study was not cited in Chapter 2 in the review of toluene-specific effects (consistent with the handling of other papers dealing with solvent mixtures).*

CHAPTER 3. HEALTH EFFECTS

COMMENT: In the subheading **3.1, INTRODUCTION**, in the audience of this profile, should be included employers, workers who handle and manipulate toluene, or mixtures of organic solvents that include toluene, and personalities that represent these workers, and other labour organized groups.

RESPONSE: *The introduction section is a standard "boilerplate" section that is the same for all toxicological profiles. The "audience" is not altered to be chemical-specific. ATSDR will consider allowing for chemical-specific audiences during the next revision of the ATSDR profile format.*

COMMENT: On the other hand, despite my limitations in toxicology, I think the referred studies in the text in this chapter enough describe the most relevant data. The limitations of each study depend on whether there is doubt by those who want to analyze these in greater depth, and the purpose of its review; in the same sense, the way that the data were treated statistically also depends on the critical reading that takes place; this constitutes an invitation to review extensively the original reference in the literature or definitely put in contact with the author. In general, the articles related to the toluene NOAELs and LOAELs, accomplish these satisfactorily.

RESPONSE: *No revisions were suggested.*

COMMENT: I think the effect of **DEATH (3.2.1.1)**, in the point **3.2.1 Inhalation Exposure** might be better described at the last of this route of exposure; furthermore, the so-called Overview and Cardiovascular Effects, begins with the deadly effects of inhaled toluene, and these observations should be more well recorded in the same subheading of **DEATH (3.2.1.1).**

RESPONSE: *The subsections are presented in the standard order used for ATSDR profiles. Regarding "deadly effects of inhaled toluene" studies cited in the Cardiovascular section, both of these human studies (Anderson et al. 1982; Shibata et al. 1994) were included in the Death section of the reviewed draft. Therefore, no revisions were required.*

COMMENT: As relates to the persistent controversy over hematological effects by the exposure to toluene, or to a mixture of this with other solvents, especially when is with benzene (Line 20 on page 40), I would kindly request just mark the bibliographic reference of Haro et al (2012): Haro-García L, Vélez-Zamora N, Aguilar-Madrid G, Guerrero-Rivera S, Sánchez-Escalante V, Muñoz SR, Mezones-Holguín E and Juárez-Pérez C. Blood disorders among workers exposed to a mixture of benzene-toluene-xylene (BTX) in a Paint Factory. Rev Peru Med Exp Salud Publica 2012;29(2):181-187.

RESPONSE: *Please refer to previous response regarding the translation of foreign language studies.*

COMMENT: Furthermore, from my particular point of view, the study of Yamamoto et al (2009) (Line 15, page 59) is excessively detailed and even seems out of the style of the rest of the document, and the conclusion reached is nor extraordinary at all and not entirely unique; I would make the same comment about how was described in the "Profile" the work of Win-Shwe et al (2010b) on line 12 on page 62.

RESPONSE: *There are several studies in this section reported in the style and/or detail of Yamamoto et al. (2009), including Fujimaki et al. (2011) and Win-Shwe et al. (2010a, 2010b). This particular series of immunological studies included a large number of end points that needed to be reported; however, since various end points and results differed between studies, there was not a logical way to condense them. The use of bullets in conveying information was determined to be the most efficient and effective way of communicating results from these studies.*

COMMENT: In BAEPs (Line 22, page 72) when speaking about the ***Auditory System Effects*** (Line 5, page 71), I kindly request the inclusion the Juárez-Pérez et al (2014) findings mentioned previously in this document. In workers exposed to toluene at low concentrations (TWA median identified for toluene was 13.14 mg/m^3 in 134 subjects at 14 workplace in a paint factory), difference was observed between right and left ear mean latencies (BAEPs) in waves I, III and V and I-V intervals, I-III and III-V, in workers exposed to a mixture of solvents that included toluene vs non-exposed workers. Multiple linear regression models for waves were performed for waves and interpeak interval latencies for both ears. An increase in latencies was observed in the exposed group.

RESPONSE: *As indicated previously, the provided reference was reviewed and added to Section 3.2.1.4, Neurological Effects - Occupational Exposure (pp.72-73)(page 131 in draft 4). Due to concurrent exposure to 13 other solvents, the conclusions that can be drawn about toluene toxicity from this study are limited (this limitation is noted in the text).*

COMMENT: I think in point **3.2.1.5 Reproductive effects** (Line 20, page 90) may well also be referred to those findings described by Miranda-Figueroa et al. (2013), which were already mentioned previously in this document.

RESPONSE: *Please refer to previous response regarding the translation of foreign language studies.*

COMMENT: Regarding the question of whether appropriate statistical tests are used in the interpretation of studies, the Reviewer commented: "As to whether the statistical tests are appropriate or not for the interpretations of the studies, it is difficult to determine. This would require an exhaustive analysis of each of the works and bibliography contemplated by the "Profile"."

RESPONSE: *No revisions were suggested.*

Levels of Significant Exposure (LSE) Tables and Figures

COMMENT: Regarding the question of whether the LSE tables and figures are complete and self-explanatory, the Reviewer commented: "This may depend on the requirements of those who read or their study needs, or the problem to address and resolve. I would not presume to offer any suggestions in advance when the document displayed figures and tables in some measure as a friendly overview of the **Levels of Significance Exposure**.

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer agrees with the categorization of "less serious" and "serious" effects cited in the LSE tables, the Reviewer commented: "In general, I could agree with the categorization "less serious" or "serious"; I also agree that is a somewhat qualitative classification and probably very "soft", but the "Profile" defined it in that way, and only the scientific community in the branch or an expert consensus would be who finally accept or not this categorization. Although it may be debatable and questionable, I must assume that this categorization was proposed by a specialized group and therefore is totally respectable. Besides, be understood that this categorization is for better profit and benefit for the general public, and the purpose of the "Profile" is not strictly intended only for qualified personnel in the field."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the MRLs are justifiable and if no MRLs were derived, do the data support deriving MRLs, the Reviewer commented: "Also be understood that the MRL are estimates and should be viewed as screening levels, and by that, I consider, by my position in Public Health, that these observations would be retained. It should be noted further that the "Profile" is a document that is of interest to the United States of America, and although is not explicitly its purpose, this becomes in an unavoidable international reference that gives framework for research in other countries, some with substantial lags of this order, so these estimators contribute to the conformation and fulfillment of regulations in those countries or regions, and encourage the generation of local but meaningful knowledge and the consequent settlement of regulations and preventive measures in the field."

RESPONSE: *No revisions were suggested.*

Evaluation of Text

COMMENT: Regarding the question of whether the major limitations of the studies have been adequately and accurately discussed, the Reviewer commented: "I must insist that to assess the limitations of a study and discuss more precisely would require a critical reading of each of the articles separately. I could hardly say the seated by the "Profile" that these actions were taken literally. On the other hand, I must admit my limitations and poor knowledge to evaluate studies with experimental animals, so I cannot issue more judgments. With respect to human health, I think the document elicits in the aim to produce or generate greater awareness in both, occupational and environmental field, in diverse human groups from different age groups."

RESPONSE: *No revisions were suggested.*

COMMENT: About the chapters of **GENOTOXICITY**, **TOXICOKINETICS,** and sections **MECHANISM OF ACTION**, **TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS,** and **CHILDREN SUSCEPTIBILITY,** I have no further comments, largely because my short expertise on all these issues.

RESPONSE: *No revisions were suggested.*

Section 3.8. BIOMARKERS OF EXPOSURE AND EFFECT

COMMENT: As regards the **BIOMARKERS OF EXPOSURE AND EFFECT** section, the document is tacit in indicate the no to date biomarkers of effect for exposure to toluene, and on the contrary, it is stated on the diversity to identify directly toluene, hippuric acid and ortho-cresol as biomarkers of exposure, and discuss about them with caution and reserve. The text does not require, in my opinion, any change.

RESPONSE: *No revisions were suggested.*

Section 3.9. INTERACTIONS WITH OTHER CHEMICALS

COMMENT: In terms of **INTERACTIONS WITH OTHER CHEMICALS** section, the text emphasizes the importance and relevance of the mixture of toluene with benzene and xylene, among others.

RESPONSE: *No revisions were suggested.*

Section 3.10. POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

COMMENT: With respect to section **POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE**, I'm not sure if the addressed point abounds in the biologist attitude and does not include others; for example, take into account individuals with pre-existing psychological or psychiatric disorders, or with adverse social conditions, such as poverty, addiction to illegal drugs, alcoholism, having a precarious job, being illiterate, be migrant workers who does not speak or read English language well, undergo malnutrition, obesity or other feeding disorders, live in highly polluted urban areas or in boundary with

highly industrialized areas. However, I accept that the discussion that takes place in the text must also be considered.

RESPONSE: *The meaning of these comments is not entirely clear; while there are medical and social conditions which may generally make some individuals more susceptible to chemical exposures, Section 3.10 attempts to describe the known evidence for a particularly susceptible population specifically to toluene. It is uncertain if the Reviewer is requesting a change; it appears that they are not and accept the discusstion as is. Therefore, no changes were made.*

Section 3.11. METHODS FOR REDUCING TOXIC EFFECTS

COMMENT: As relates **METHODS FOR REDUCING THE TOXIC EFFECTS** section, I believe that those listed are somewhat general, but I agree with them; perhaps should be pointed out whether these measures should be modified if any pre-existing condition that could worsen the current intoxication; in fact, should be taken into account so far the description mentioned in the previous section **POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE**.

RESPONSE: *ATSDR agrees that this section describes general methods that are not specific to toluene; however, at this time, there are not any special protocols for reducing toxic effects of acute toluene exposure. No changes were made in response to the comment.*

COMMENT: Although I did not warn disputes, I would do greater emphasis on actions that should not be performed, such as contraindicate the emesis, or to consider any previous or current medication and/or history of addiction or consumption of illicit drug, among other backgrounds. This section should somehow highlight that the mentioned methods are to reduce only acute toxic effects.

RESPONSE: *In response to this comment, the text was edited to indicate that methods are for acute exposures.*

Section 3.12. ADEQUACY OF THE DATABASE

COMMENT: With respect to the **ADEQUACY OF THE DATA BASE** section, I do not notice biased information, in fact the document refers to the presence of incomplete data, which has limitations, or this or that point needs to be investigated further. Throughout all the text itself, the wider gap of knowledge regarding the toxicity acquired by the oral or dermal route is highlighted; even that is through respiratory route, states that it needs to be better documented nevertheless the abundance in the information on this issue, in large degree because the wide variability in the human response. From my particular point of view, still is necessary to generate more and better information to be included in larger and more diverse populations.

RESPONSE: *The meaning of these comments is not entirely clear. The reviewer appears to agree with the summary of existing data and that more and better information is still necessary as described in 3.12.2.No changes were made.*

COMMENT: Regarding the question of whether the text adequately justifies why further development of the data needs would be desirable or justifies the inappropriateness of developing the data need at present, the Reviewer commented: "I must confess that the last question listed in this section, to me was

so confusing; however, I think that the text adequately justify further development of the data need would be desirable."

RESPONSE: *No revisions were suggested.*

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

COMMENT: Regarding the questions for Chapter 4, the Reviewer commented: "No comment."

RESPONSE: *No revisions were suggested.*

CHAPTER 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

COMMENT: Regarding the questions for Chapter 5, the Reviewer commented: "No comment."

RESPONSE: *No revisions were suggested.*

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

COMMENT: The vision of this chapter is such as local issue of great interest to the people of the United States, but encouraged to conduct similar analyzes in other countries or regions of the world.

RESPONSE: *Revisions in response to this comment were not made. ATSDR toxicological profiles focus on U.S. exposures in response to mandates from U.S. Congress.*

COMMENT: The name of the subheading seems to me some unfortunate, since it also deals with the points of toluene release and its environmental fate, and not just regarding the potential for human exposure.

RESPONSE: *As previously mentioned, headings and subheadings are standard in all ATSDR profiles. Information such as release, environmental fate, levels monitored in the environment, etc., affect the potential for exposure. Nevertheless, ATSDR will consider these suggestions during the next revision of the ATSDR profile format.*

COMMENT: Under this framework, it is almost a presumptuousness to mention that the theoretical and technical supports are sufficient, since the same text clarifies that the available data should be taken with caution because only certain types of settlements and businesses report the Toxic Release Inventory (**TRI**). Likewise I daresay in the same way corresponding to the other data included in this chapter.

As regards the transport and partitioning in the Environmental Fate (**6.3**) subchapter I have no further comment, and the considerations on the mixture of BTEX seem considerable wisdom, however, with regard to discharges of toluene, for example in water, it seems not have been treated as thoroughly as those found in air, although it is understood that mostly occur at that field; my appreciation is the same with soils, and although they are almost qualified as negligible from an environmental point of view, they are important alike.

RESPONSE: *No revisions were suggested.*

COMMENT: I could hardly review from a technical point of view if the units in the toluene levels that monitors in the environment are the most appropriate, and whether they are appropriate by the media to analyze; honestly, I do not know some of them, or I have never handled, as "... parts per billion of carbon (ppbC) ...

RESPONSE: *No revisions were suggested.*

COMMENT: In the General Population and Occupational Exposure section, the text is enough explicit in the description of sources and pathways of exposure, and those considered with potentially high exposures. Although I agree with these kinds of populations, I notice a predilection—and it is understandable—for evaluating and analyzing the exposure on children.

RESPONSE: *No revisions were suggested.*

COMMENT: Section **6.8, ADEQUACY OF THE DATABASE**, I think it is presented in a neutral manner and I not warn biases, however, on page 249, in Exposure Levels in Human, states that "... Toluene exposure in the workplace is well documented ... "; I'm not in total agreement with this view, perhaps exposure to toluene in the workplace is at the moment widely documented, but do not qualify as "... well documented ..."; making judgments of this kind could admonish that further inquiry about health effects from exposure to toluene at work not be carried out, when in fact still there are aspects that are not well elucidated, there are still controversies and exist possible effects, although subtle, not identified yet.

RESPONSE: *This particular section is referring to adequacy of the data for human exposure, not human health effects. Data needs for health effects are covered in Section 3.12. The sentence was revised to read: "Toluene exposure <u>levels</u> in the workplace . . ." for clarity.*

COMMENT: I have no signs on **6.8.2, Ongoing studies**; the little content in this point maybe is linked with my previous comment.

RESPONSE: *No revisions were suggested.*

COMMENT: The information displayed in the various tables of this chapter is truly enviable. Perhaps it should be noted and suitable that there is very little and poor literature—and probably none—related to health effects due to inhalation exposure to toluene vapors in children.

RESPONSE: *This particular section is referring to adequacy of the data for human exposure, not human health effects. Data needs for health effects are covered in Section 3.12.*

<u>CHAPTER 7. ANALYTICAL METHODS</u>

COMMENT: I do not know if there are additional methods that can be added to the tables presented in this chapter; the included contemplate correctly the analysis of metabolites referred throughout the text. I think the issue of sampling, both biological materials such as the environmental, are sufficiently mentioned, but should be an invitation for conduct a more thorough literature search by whomever to sample toluene.

RESPONSE: *No revisions were suggested.*

COMMENT: The chapter does not appear to be biased and is presented in neutral way, and in non-judgment-fashion; I agree with the data needs and the text indicates whether any information on the data needs exists. Also the text adequately justify why further development of the data need would be desirable.

RESPONSE: *No revisions were suggested.*

CHAPTER 8. REGULATIONS AND ADVISORIES

COMMENT: Regarding the question of whether the Reviewer is aware of other regulations or guidelines that may be appropriate for Table 8-1, the Reviewer commented: "In the regulations listed under "international" I think that could be included the List of MAK and BAT Values 2013, Maximum Concentration and Biological Tolerance values at the Workplace, Report No. 49, Die Deutsche Bibliothek – CIP-Cataloguing-in-Publication- Data, ISBN: 978-3-527-33616-6, 2013; WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, Printed in the Federal Republic of Germany, which states that the maximum concentration to which workers can be exposed to toluene in the workplace should be 190 mg/m^3 [milligram (mg) of toluene per cubic meter (m^3) of air].

RESPONSE: *MAK and BAT values were not added to Table 8-1. This table includes values from International Agencies and U.S. National Agencies. For the purposes of this document, ATSDR does not search for foreign national regulations, advisories, or guidelines.*

CHAPTER 9. REFERENCES

COMMENT: Regarding the question of whether there are additional references that provide new data or if there are better studies than those already in the text, the Reviewer commented: "Copies of the references already mentioned in the other chapters are provided."

RESPONSE: *Responses regarding additional references can be found in previous sections.*

GENERAL COMMENTS

COMMENT: The material presented seems appropriate to draw the attention of the general public—including adolescents and children—but I think the inclusion of some illustrations and extremely simple figures look with favor for the understanding of the people in these age groups and others.

RESPONSE: *ATSDR will consider this suggestion in future revisions of the toxicological profile format.*

COMMENT: I felt Chapter 3 very long, maybe if the **Health Effects** be divided into those related to occupational ambit and separate the environmental, or results in humans and what is seen in experimental animals also separately.

RESPONSE: *ATSDR believes that the length is necessary in order to provide a comprehensive review of the known health effects of toluene. Chapter 3 is organized according to a standard ATSDR template used for all toxicological profiles.*

Review comments provided by Reviewer #2:

GENERAL QUESTIONS

Reviewer 2 made several editorial suggestions throughout the review of "The Profile". Unless otherwise noted, all grammatical/language suggestions from reviewer 2 were incorporated into "The Profile", and will not be discussed individually.

COMMENT: Regarding the question of whether there are any data relevant to child health and developmental effects that have not been discussed in the profile, the Reviewer commented: "No, it appears that data relevant to child health and developmental effects have been adequately identified and discussed in the text."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are any general issues relevant to child health that have not been discussed in the profile, the Reviewer commented: "No."

RESPONSE: *No revisions were suggested.*

CHAPTER 1. PUBLIC HEALTH STATEMENT

COMMENT: Regarding the question of whether Chapter 1 presents the important information in a non-technical style suitable for the average citizen, the Reviewer commented: "Yes."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the answers to the questions in Chapter 1 adequately address the concerns of the lay public, whether the summary statements are consistent and supported by the technical discussion in the remainder of the text, the Reviewer commented: "Yes, the answers to the questions adequately addressed the concerns of the lay public. The summary statements are consistent and supported by the technical discussion in the main text."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the scientific terms used in Chapter 1 are too technical or require additional explanation, the Reviewer suggested: "p.4, under "introduction to toluene health effects", I would substitute "Nervous system effects" with "Effects on brain".

RESPONSE: *The first sentence in "How Can Toluene Affect Your Health" was edited to read: "A serious health concern is that toluene may have an effect on your nervous system (brain and nerves)."*

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

COMMENT: Regarding the question of whether the Reviewer agrees with the discussion in Chapter 2 on effects known to occur in humans, the Reviewer commented: "Yes, the known effects that occur in humans from exposure to toluene are properly reported in the text."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the effects only observed in animals are likely to be of concern to humans, the Reviewer commented: "Yes, the effects observed in animals are of concern to humans if: 1) the animal study is properly designed, 2) results (the observed effects) are consistent across studies. In addition, human relevance can be derived or excluded if a known mode of action is identified in animals."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether exposure conditions are adequately described, the Reviewer commented: "Yes, it appears that the exposure conditions have been quite adequately described in the text."

RESPONSE: *No revisions were suggested.*

CHAPTER 3. HEALTH EFFECTS

COMMENT: Regarding the question of whether adequately designed human studies are identified in Chapter 3 and if the study(ies) are not adequately designed are the major limitations of the studies sufficiently described in the text, the Reviewer commented: "Yes, several adequately designed human studies were identified for acute and chronic exposures to toluene. Others were not the case however the major limitations of these studies were sufficiently described in the text."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the conclusions drawn by the authors of the human studies are appropriate and accurately reflected in the profile, the Reviewer commented: "Yes. It appears that the conclusions drawn by the authors of the studies were appropriate and acutely reflected in the profile."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all appropriate NOAELs and/or LOAELs are identified for each human study, the Reviewer commented: "Appropriate NOAELs and/or LOAELs were identified for reliable human studies that were adequately designed. For studies lack quantitative exposure information, NOAELs/LOAELs were excluded, adequate justification for such exclusion was provided in the text."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether appropriate statistical tests are used in the human studies, the Reviewer commented: "Yes, the statistical tests used in the studies were appropriate, other statistical tests could not have been more appropriate. And yes, it appeared that the statistical results of study data were evaluated properly."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of other human studies which may be important in evaluating the toxicity of the substance, the Reviewer commented: "No."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether adequately designed animal studies are identified in the text, the Reviewer commented: "Yes."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the animal species is appropriate for the most significant toxicological endpoint of the study, the Reviewer commented: "Yes, the animal species appropriate for the most significant toxicological endpoint of the study."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the conclusions drawn by the authors of the animal studies are appropriate and accurately reflected in the text, the Reviewer commented: "Yes.", but made several editorial suggestions and the following remark: "p.83, line 30-34. Brain weights were increased in rats but not in mice treated similarly in the NTP (1990) study. A brief discussion should be added here to explain whether a mechanism is available for this difference or the mechanism is unclear."

RESPONSE: *Most editorial suggestions were incorporated as suggested; however, the word "statistically" was not removed from the text on line 3 of page 99 or lines 25-26 of page 99. Throughout the document, the phrase "statistically significant" was used to define that "significant" was not a qualitative term; rather it was defined based on statistics. Regarding the species difference for brain weight, the mechanism(s) underlying the apparent species difference in the intermediate-duration NTP study is unknown. This is now stated in the text.*

COMMENT: Regarding the question of whether all appropriate NOAELs and LOAELs are identified for each animal study and whether all appropriate toxicological effects are identified for the studies, the Reviewer commented: "Yes. All appropriate NOAELs and LOAELs identified for each study with the exception for certain end points in some studies. The reason for not identifying a NOAEL or LOAEL for these studies has been appropriately discussed in the text."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is a discussion of the toxicities of the various forms of the substance, the Reviewer commented: "Not applicable."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether appropriate statistical tests are used in the interpretation of the animal studies, the Reviewer commented: "Yes. And the statistical test results of study data were properly evaluated."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of other animal studies which may be important in evaluating the toxicity of the substance, the Reviewer commented: "No."

RESPONSE: *No revisions were suggested.*

Levels of Significant Exposure (LSE) Tables and Figures

COMMENT: Regarding the question of whether the LSE tables and figures are complete and self-explanatory, the Reviewer commented: "Yes. The LSE tables and figures are complete and self-explanatory; the "Users Guide" explains clearly how to use them; it appears that the exposure levels (units, dose) are accurately presented for the route of exposure."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer agrees with the categorization of "less serious" and "serious" effects cited in the LSE tables, the Reviewer commented: "Yes."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the MRLs are justifiable and if no MRLs were derived, do the data support deriving MRLs, the Reviewer commented: "Yes. The MRLs values that have been derived are justifiable. It was properly discussed in the text if no MRLs could be derived due to lack of date support."

RESPONSE: *No revisions were suggested.*

Evaluation of Text

COMMENT: Regarding the question of whether the major limitations of the studies have been adequately and accurately discussed, the Reviewer commented: "Yes."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the effect or key endpoint has been critically evaluated for its relevance in both humans and animals, the Reviewer commented: "Yes."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether "bottom-line" statements have been made regarding the relevance of the endpoint for human health, the Reviewer commented: "Yes."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the conclusions are appropriate given the overall database, the Reviewer commented: "Yes, the conclusions are appropriate given the overall database."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether adequate attention has been paid to dose-response relationships for both human and animal data, the Reviewer commented: "Yes. The dose-response relationships, wherever possible, in human data were appropriately discussed in the text. The dose-response relationships in animal studies were also adequately discussed in the text."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the animal data has been used to draw support for any known human effects, the Reviewer commented: "Yes, animal data has been used to support for known human health effects for toluene exposure, such support appears to be valid and appropriate.

RESPONSE: *No revisions were suggested.*

Section 3.4. TOXICOKINETICS

COMMENT: Regarding the question of whether there is an adequate discussion of absorption, distribution, metabolism, and excretion of the substances, the Reviewer commented: "Yes. It appears that the discussion of absorption, distribution, metabolism and excretion of toluene is adequate."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the major organs, tissues, etc in which the substance is stored have been identified, the Reviewer commented: "Yes."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all applicable metabolic parameters have been presented and all available PB/PK models have been presented, the Reviewer commented: "Yes."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is adequate discussion of the differences in toxicokinetics between animals and humans, the Reviewer commented: "Yes, given the limited database available for such comparisons."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is an adequate discussion of the relevance of animal toxicokinetic information for humans, the Reviewer commented: "Yes, given the limited database available for such comparisons."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is a discussion of the toxicokinetics of different forms of the substance, the Reviewer commented: "Not applicable."

RESPONSE: *No revisions were suggested.*

Section 3.5. MECHANISMS OF ACTION

COMMENT: Regarding the question of whether all possible mechanisms of action have been discussed, the Reviewer commented: "It appeared that all possible mechanisms of action including mechanisms of metabolism, absorption, distribution, and excretion, as well as mechanisms for toxicity related to toluene exposure."

RESPONSE: *No revisions were suggested.*

Section 3.8. BIOMARKERS OF EXPOSURE AND EFFECT

COMMENT: Regarding the question of whether all the biomarkers of exposure are specific for the substance or are general for a class of substances, the Reviewer commented: "The currently used biomarker of exposure for the toluene exposure is substance specific. This exposure biomarker for toluene, recommended by ACGIH (2010, 2013), includes combination of three biomarkers: ortho-cresol (toluene metabolite), unchanged toluene levels in urine at the end of a workshift, and toluene levels in blood immediately prior to the last shift of a workweek."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are valid tests to measure the biomarkers of exposure, the Reviewer commented: "Valid tests available to measure the biomarkers of exposure of toluene and is consistent with statements made in other sections of the text.

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are valid tests to measure the biomarkers of effect, the Reviewer commented: "It seems that there are no specific biomarkers available for toluene

exposure. The authors have discussed this in the "profile"."

RESPONSE: *No revisions were suggested.*

Section 3.9. INTERACTIONS WITH OTHER CHEMICALS

COMMENT: Regarding the question of whether there is an adequate discussion of the interactive effects with other substances, the Reviewer commented: "It appears that the interactive effects of toluene with other substances have been adequately discussed in this section. The discussion has concentrated on the effects that might occur at the hazardous waste sites with briefly discussion of interaction with drug therapy which applies to environmental or occupational exposure to toluene at the hazardous waste sites."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text discusses the mechanisms of interactions with other substances, the Reviewer commented: "The known mechanisms of interaction of toluene with other substances are properly discussed in the text."

RESPONSE: *No revisions were suggested.*

Section 3.10. POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

COMMENT: Regarding the question of whether there is a discussion of populations at higher risk because of biological differences which make them more susceptible, the Reviewer commented: "A discussion of populations at higher risk because of biological differences which make them more susceptible is properly described in this section. The selection of population seems appropriate and reasons for such selection seem valid. No additional studies regarding the population susceptibility to toluene exposure are located."

RESPONSE: *No revisions were suggested.*

Section 3.11. METHODS FOR REDUCING TOXIC EFFECTS

COMMENT: Regarding the question of whether the management and treatment discussed in Section 3.11 is specific for the substance or is general for a class of substances, the Reviewer commented: "There is no specific treatment for toluene-induced health effects. Only general guidelines are recommended for reducing the acute toxicity of toluene exposure"

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is any controversy associated with the treatment and whether it is well accepted, the Reviewer commented: "There is a controversy of using emesis in treating patients of toluene ingestion due to risk of aspiration; this is not a well-accepted treatment for toluene exposure."

RESPONSE: *No revisions were suggested. The profile states that emesis is contraindicated in cases of toluene ingestion.*

COMMENT: Regarding the question of whether there are any hazards associated with the treatment of populations that are unusually susceptible to the substances, the Reviewer commented: "It is not discussed in text whether there are any hazards associated with the treatment of populations that are unusually susceptible to the substance, if any, this should be included in this section."

RESPONSE: *To our knowledge, there are not any special protocols for reducing toxic effects of acute toluene exposure in susceptible individuals.*

COMMENT: Regarding the question of whether there are treatments available to prevent the specific substance from reaching the target organ, the Reviewer commented: "There is no specific treatment available to prevent toluene from reaching target organs. Only general approaches can be recommended, such as oxygen therapy, positives-pressure ventilation, fluid consumption and renal dialysis."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is any controversy associated with the treatment for preventing the substance from reaching the target organ, the Reviewer commented: "Yes, the use of oxygen therapy may increase the rate of oxidative metabolism of toluene leading to increased production of toxic metabolites that results in treatment related adverse effects." The Reviewer also had the following comment: "p.187, line 9-10. It is not clear what the "positive effect on the rate of oxidative metabolism…" really means. My understanding is that increased oxygen availability would increase the rate oxidative metabolism, therefore increased production of oxidized toluene metabolites leading to increased toxicity. If not so, this should be rewritten accordingly."

RESPONSE: *This sentence was deleted.*

COMMENT: Regarding the question of whether there are any hazards associated with the treatment for preventing the substance from reaching the target organ in populations unusually susceptible to the substance, the Reviewer commented: "No."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are any treatments to prevent adverse effects as the substance is being eliminated from the major organs/tissues where it has been stored, the Reviewer commented: "No."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are treatments available to prevent the specific substance from reaching the target organs, the Reviewer commented: "No specific treatments are available to prevent toluene or it's metabolites from reaching the target organs. Recommended approaches are general for a class of substances."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is any controversy associated with the treatment to prevent the substance from reaching target organs, the Reviewer commented: "No, given the limited information provided in the text."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are any hazards associated with treatment to prevent the substance from reaching target organs in populations unusually susceptible to the substance, the Reviewer commented: "No, given the limited information provided in the text."

RESPONSE: *No revisions were suggested.*

Section 3.12. ADEQUACY OF THE DATABASE

COMMENT: Regarding the question of whether the Reviewer knew of other studies which may fill a data gap, the Reviewer commented: "No. It appears that the authors of this document have done a fairly exhaustive literature review and I am not aware of any additional studies that may fill a data gap."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the data needs are presented in a neutral, non-judgmental fashion, the Reviewer commented: "Yes."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer agrees with the identified data needs, the Reviewer commented: "Yes, the identified data needs seem appropriate."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text indicates whether any information on the data need exists, the Reviewer commented: "Yes."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text adequately justifies why further development of the data needs would be desirable or justifies the inappropriateness of developing the data need at present, the Reviewer commented: "Yes."

RESPONSE: *No revisions were suggested.*

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

COMMENT: Regarding the question of whether the Reviewer is aware of any chemical and physical property information or values that are wrong or missing, the Reviewer commented: "No."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether information was provided on the various forms of the substance, the Reviewer commented: "Not applicable"

RESPONSE: *No revisions were suggested.*

CHAPTER 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

COMMENT: Regarding the question of whether the Reviewer is aware of any information on the production, import/export, use or disposal of the substance that is wrong or missing, the Reviewer commented: "No."

RESPONSE: *No revisions were suggested.*

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

COMMENT: Regarding the question of whether the text appropriately traces the substance from its point of release to the environment until it reaches the receptor population, the Reviewer commented: "Yes, text appropriately traced toluene from its point of release to the environment until it reaches the receptor population. Sufficient and technically sound information regarding the extent of occurrence at NPL sites are provided in the text. No other relevant information was located."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text covers pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media, the Reviewer commented: "Yes, it appears that pertinent information relative to transport, partitioning, transformation, and degradation of toluene in all media is covered in the text. No other relevant information was located."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text provides information on levels monitored or estimated in the environment (including background levels), that proper units are used for each medium, and that the information includes the form of the substance measured, the Reviewer commented: "Yes, these information were provided with proper unites used for each medium. It appears that the quality of the information was adequately discussed in the text. No other relevant information was identified."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text describes sources and pathways of exposure for the general population, occupations involved in the handling of the substance, and populations with potentially high exposures, the Reviewer commented: "Yes, the text described the sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures. The selection of these populations is appropriate."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the questions about the Identification of Data Needs and Ongoing Studies sections in the Human Exposure Chapter, the reviewer had no additional suggestions for revision.

RESPONSE: *No revisions were suggested.*

CHAPTER 7. ANALYTICAL METHODS

COMMENT: Regarding the question of whether the Reviewer is aware of additional methods that should be added to the profile, the Reviewer commented: "No."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the methods have been included for measuring key metabolites previously mentioned in the text, the Reviewer commented: "Yes."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether unique issues related to sampling for the substance exist and have been adequately addressed in the text, the Reviewer commented: "Yes."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the questions about the Identification of Data Needs and Ongoing Studies sections in the Analytical Methods Chapter, the reviewer had no additional suggestions for revision.

RESPONSE: *No revisions were suggested.*

CHAPTER 8. REGULATIONS AND ADVISORIES

COMMENT: Regarding the question of whether the Reviewer is aware of other regulations or guidelines that may be appropriate for Table 8-1, the Reviewer commented: "No."

RESPONSE: *No revisions were suggested.*

CHAPTER 9. REFERENCES

COMMENT: Regarding the question of whether there are additional references that provide new data or if there are better studies than those already in the text, the Reviewer commented: "No, not to my knowledge."

RESPONSE: *No revisions were suggested.*

UNPUBLISHED STUDIES (IF APPLICABLE TO REVIEW)

COMMENT: Regarding the question on unpublished studies, the Reviewer commented: "The following reference was identified as unpublished in the supporting document:

API. 1992. Initial submission: A preliminary study of the effect of toluene on pregnancy of the rat (inhalation exposure). Final report with cover letter dated 072292. Washington, DC: American Petroleum Institute. Submitted to U.S. Environmental Protection Agency under TSCA Section FYI. APT191309. OTS0000857.

This study was adequately designed. The methods used were appropriate. The reporting of results and their interpretation by the author are reasonable. I agree with the interpretation of the author.

RESPONSE: *No revisions were suggested.*

Review comments provided by Reviewer #3:

GENERAL QUESTIONS

Reviewer 3 made several editorial suggestions throughout the review of "The Profile". Unless otherwise noted, all grammatical/language suggestions from were incorporated into "The Profile", and will not be discussed individually.

COMMENT: Regarding the question of whether there are any data relevant to child health and developmental effects that have not been discussed in the profile, the Reviewer commented: "In my opinion, the report provides the necessary data relevant to children's health and developmental effects. The report provides a detailed discussion of the potential health effects of toluene exposure in humans from conception to 18 years of age (Chapter 1 and Section 3.7) as well as a section on sources of exposures (Section 6.6). The report also contains several sections on how parents/guardians might protect against such effects."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are any general issues relevant to child health that have not been discussed in the profile, the Reviewer commented: "In my opinion, the profile of toluene effects is very thorough. I'm not aware of any general issues relevant to child health that have not been discussed in the profile."

RESPONSE: *No revisions were suggested.*

CHAPTER 1. PUBLIC HEALTH STATEMENT

COMMENT: Regarding the question of whether Chapter 1 presents the important information in a non-technical style suitable for the average citizen, the Reviewer commented: "In my opinion, the tone of the chapter is factual and not judgmental. The important information is presented in a non-technical style suitable for the average citizen. I do have several suggestions for improving the text which are presented in the answer to the next question."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the answers to the questions in Chapter 1 adequately address the concerns of the lay public, whether the summary statements are consistent and supported by the technical discussion in the remainder of the text, the Reviewer commented: "Yes, the answers to the questions adequately address the concerns of the lay public. I found the summary statements to be consistent and well supported by the technical discussions in the text that followed. I do have several suggestions on improving the text."

> **SUGGESTION:** On page 3, within the section "How toluene enters your Body", it's not clear to me why the last sentence within the "Air, Possible Exposure Pathway" is limited to just paint thinner, because a number of products containing toluene are abused including airplane glue, nail polish, gasoline, etc. May I suggest changing or adding the phrase, "products containing toluene." Also the references used here are dated and more importantly, the Midford reference doesn't mention paint. May I suggest three recent reviews [Bowen 2011; Garland et al. 2011; Howard et al. 2011]?

RESPONSE: *Changes were incorporated as suggested.*

SUGGESTION: On page 4, within the section "Introduction to toluene health effects", the sentence that begins, "High levels of toluene exposure during pregnancy…", it is not clear to me why the "EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version" is used as a reference here. Unless I missed something, there is nothing in this document regarding high levels of toluene exposure during pregnancy. I would suggest replacing this reference with a recent review of this topic [Hannigan and Bowen 2010]?

RESPONSE: *The EPA reference was cited incorrectly to the "Toxic chemical release inventory reporting forms and instructions;" it should have been a citation for the 2005 IRIS Toxicological Profile for Toluene. However, the EPA (2005) reference has been replaced with Hannigan and Bowen (2010), as well as Bowen (2011), as these are more recent papers specifically reviewing the risk of high exposure levels during pregnancy.*

SUGGESTION: On page 4, within the section "Short term exposure effects", the sentence which reads, "If you are exposed to a large amount of toluene in a short time because you deliberately sniff paint or glue, you will first feel light-headed." concerns me because it doesn't reflect the level of danger associated with this activity. May I suggest, "One very dangerous activity is to expose yourself to a large amount of toluene in a short time because you deliberately inhaled/sniffed paint or glue. At first you will feel light-headed. If exposure continues, you can become dizzy, sleepy, or unconscious …"

RESPONSE: *Changes were incorporated as suggested.*

SUGGESTION: On page 4, within the section "Short term exposure effects", the sentence that begins, "You might even die" some of these references are quite dated. May I suggest adding Bowen et al. 1999?

RESPONSE: *Changes were incorporated as suggested. Bowen et al. (1999) was also added to Section 3.2.1.1, Death (p. 34).*

SUGGESTION: On page 6, within the section "Exposure effects for children generally", the sentence that reads, "Older children and adolescents may be exposed to toluene if they breathe household products containing it to get high (McCann 1992; Young 1987)." the McCann reference isn't about abusing toluene but general exposure to toxic materials in art supplies.

RESPONSE: *The McCann reference was removed and Howard et al. (2011) and Garland et al. (2011) were cited in its place.*

SUGGESTION: On page 6, the sentence that reads, "Some older children and adolescents who have repeatedly breathed large amounts of toluene to get high have developed loss of muscle control, loss of memory, poor balance, and decreased mental (Byrne et al. 1991; Devathasan et al. 1984; King et al. 1981)." Decreased mental what? Should this read "decreased mental abilities"? or capabilities? Also consider adding/replacing references with Scott and Scott (2012, 2014).

RESPONSE: *The text has been edited to read "decreased mental abilities." The Scott and Scott (2012, 2014) references have been added.*

SUGGESTION: On page 7, the sentence that reads, "Some mothers who breathed large amounts of toluene during pregnancy to get high have had children with birth defects, including retardation of mental abilities and growth (ACGIH 2007; EPA 2005)." Again, I don't understand the use of the EPA 2005 reference on "Toxic chemical release inventory reporting forms and instructions". May I suggest replacing with one or more of the following references [Bowen 2011; Hannigan and Bowen 2010; Jones and Balster 1998]?

RESPONSE: *As mentioned above, the EPA reference was cited incorrectly to the "Toxic chemical release inventory reporting forms and instructions;" it should have been a citation for the 2005 IRIS Toxicological Profile for Toluene. Both the ACGIH and EPA references have been replaced by the suggested citations that are more focused on inhalation abuse during pregnancy.*

SUGGESTION: On page 7, the sentence that reads, "Results from animal studies have found similar effects in new born animals that had mothers that breathed large amounts of toluene during pregnancy" needs a reference. May I suggest one or more of the following references: [Bowen 2011; Hannigan and Bowen 2010; Jones and Balster 1998]?

RESPONSE: *Hannigan and Bowen (2010) and Jones and Balster (1998) were cited, along with ACGIH (2007) and the 2005 IRIS toxicological profile. Bowen (2011) was not cited, as animal studies were not reviewed in detail.*

COMMENT: Regarding the question of whether the scientific terms used in Chapter 1 are too technical or require additional explanation, the Reviewer commented "On page 5, I think the terms 'carcinogenicity' and/or 'carcinogenic' need to be explained or defined. I would suggest rewriting the sentence preceding these terms, 'Studies in workers and animals exposed to toluene generally indicate that toluene does not cause cancer (ACGIH 2007; EPA 2005).' could be 'Studies in workers and animals exposed to toluene generally indicate that toluene is not carcinogenic (cancer-causing) (ACGIH 2007; EPA 2005).' Again, I don't understand the use of the EPA 2005 reference on 'Toxic chemical release inventory reporting forms and instructions'."

RESPONSE: *Language changes were incorporated as suggested. The EPA reference was cited incorrectly to the "Toxic chemical release inventory reporting forms and instructions;" it should have been a citation for the 2005 IRIS Toxicological Profile for Toluene. This has been corrected throughout Chapter 1.*

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

COMMENT: At first it was not clear to me why a "Canadian soil quality guidelines…" reference was used to document the sentence "Toluene is a clear colorless liquid possessing high vapor pressure and low to moderate water solubility (CCME 2004)". I realized that the reference is incomplete (missing "Toluene") and as a result references another article. The reference should read:

CCME. 2004. Canadian soil quality guidelines for the protection of environmental and human health: Toluene (2004). In: Canadian environmental quality guidelines, 1999, Canadian Council of Ministers of the Environment, Winnipeg.

RESPONSE: *The citation was fixed.*

COMMENT: On page 13, the sentence, "Cardiac edema and congestion were observed in rats given single gavage doses of 5,200 mg/kg, compared with controls (Tas et al. 2013b)" the dose was reported as 6 mL/kg/gavage in the paper. Was this converted?

RESPONSE: *Yes, the dose was converted using the following equation: dose (6 mL/kg) × density (866.9 mg/mL) = 5,201.4 mg/kg. This information was reported in the supplemental document.*

COMMENT: Regarding the question of whether the Reviewer agrees with the discussion in Chapter 2 on effects known to occur in humans, the Reviewer commented: "Yes, I agree with the effects known to occur in humans as reported in the text. The section on Endocrine effects may benefit from the following reference which suggests that compounds in fuels and some solvents (toluene) may act as reproductive endocrine disruptors."

Susan R Reutman, Grace Kawas LeMasters, Edwin A Knecht, Rakesh Shukla, James E Lockey, G Edward Burroughs, and James S Kesner. 2002. Evidence of reproductive endocrine effects in women with occupational fuel and solvent exposures. Environ Health Perspect. Aug 2002; 110(8): 805–811. PMCID: PMC1240953.

RESPONSE: *The provided reference was reviewed and added to Chapter 3.2.1.3 (pp. 92-93). Because the analysis was of BTEX, not toluene, this study was not discussed in Chapter 2 (consistent with the handling of other papers dealing with solvent mixtures).*

COMMENT: Regarding the question of whether the effects only observed in animals are likely to be of concern to humans, the Reviewer commented: "Yes, the effects only observed in animals are likely to be of concern to humans. Support for this comes from toluene inhalation studies in which animals demonstrate changes in behavior, hearing loss, and subtle changes in brain structure, electrophysiology, and levels of neurotransmitters which have also been observed in humans. Other toluene effects of concern include the immune system, liver, kidney, as well as developmental effects."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether exposure conditions are adequately described, the Reviewer commented: "Yes, exposure conditions have been adequately described. In addition, there are several areas where there is limited data available for humans (i.e., respiratory effects following oral exposure, gastrointestinal effects following oral exposure, endocrine effects of toluene exposure, immunological effects of toluene in humans). These areas are properly identified in the text."

RESPONSE: *No revisions were suggested.*

CHAPTER 3. HEALTH EFFECTS

COMMENT: On page 56, lines 17-22, there is a very long sentence that doesn't make sense to me. I'm not sure if something is missing or what. Consider rewriting? The sentence is, "Associated toluene-induced significant changes in plasma nerve growth factor (NGF) and mRNA levels for neurotrophins and receptors in lungs in allergy-challenged mice were increased plasma NGF in 9-ppm mice (~200% increased) and decreased lung levels of mRNA for brain-derived nerve factor (BDNF, ~40% decreased) and tropomyosin-related kinase A (Trk A, ~50% decreased) in 9- and 90-ppm mice; no significant exposure-related changes were found in lung levels of mRNAs for NGF, neurotrophin-3 (NT-3), or Trk B."

RESPONSE: *The sentence was edited for clarification: "In allergy-challenged mice, toluene exposure led to several significant biochemical changes in the lungs, including increased plasma NGF in 9-ppm mice (~200% increased) and decreased lung levels of mRNA for brain-derived nerve factor (BDNF, ~40% decreased) and tropomyosin-related kinase A (Trk A, ~50% decreased) in 9- and 90-ppm mice; no significant exposure-related changes were found in lung levels of mRNAs for NGF, neurotrophin-3 (NT-3), or Trk B." (Correction on page 115).*

COMMENT: Regarding the question of whether adequately designed human studies are identified in Chapter 3 and if the study(ies) are not adequately designed are the major limitations of the studies sufficiently described in the text, the Reviewer commented: "Yes, there were adequately designed human studies identified in the text with the exception of the sections where no human studies exist (i.e., oral administration and the health effects that may follow, intermediate-duration exposure in humans, etc.). However, when human studies of toluene do not exist it was pointed out in the text."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the conclusions drawn by the authors of the human studies are appropriate and accurately reflected in the profile, the Reviewer commented: "Yes, the conclusions drawn by the authors of the studies are accurately and appropriately reflected in the profile."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all appropriate NOAELs and/or LOAELs are identified for each human study, the Reviewer commented: "Yes, the appropriate NOAELs and/or LOAELs were identified for each study."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether appropriate statistical tests are used in the human studies, the Reviewer commented: "This is a difficult question to answer without going back through and reading all of the studies cited, several of which I don't have access. Although not a perfect system, one would hope that as peer-reviewed publications, reviewers of these articles would have checked to make sure that the proper statistical tests had been used. However, for the studies that I was able to review (which was quite a few), it appears as though the appropriate statistical tests were used."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of other human studies which may be important in evaluating the toxicity of the substance, the Reviewer commented: In section 3.2.1.5, the Reproductive Effects section may benefit from the following reference which suggests that compounds in fuels and some solvents (toluene) may act as reproductive endocrine disruptors:

Susan R Reutman, Grace Kawas LeMasters, Edwin A Knecht, Rakesh Shukla, James E Lockey, G Edward Burroughs, and James S Kesner. 2002. Evidence of reproductive endocrine effects in women with occupational fuel and solvent exposures. Environ Health Perspect. Aug 2002; 110(8): 805–811. PMCID: PMC1240953

RESPONSE: *As stated above, the provided reference was reviewed and added to Section 3.2.1.5, Reproductive Effects (pp. 92-93). Due to concurrent exposure to jet fuels and other solvents, the conclusions that can be drawn about toluene toxicity from this study are limited (this limitation is noted in the text).*

COMMENT: Regarding the question of whether adequately designed animal studies are identified in the text, the Reviewer commented: "The majority of the animal studies presented were adequately designed and carried out. While I understand the importance of reporting the toxicological results from, 'Tas U, Ekici F, Koc F, et al. 2013b. Acute cardiotoxic effects of high dose toluene: An experimental study. Anadolu Kardiyol Derg 13(1):3-8.', in my opinion this study suffers from an insufficient number of dose groups (a control and one very high toluene group (6 mL/kg/gavage) which makes it very difficult to derive any type of dose-effect for toluene (NOAELs not possible). A similar argument can be made for the, 'Ayan M, Tas U, Sogut E, et al. 2013. The apoptotic effect of a high dose of toluene on liver tissue during the acute phase: An experimental study. Toxicol Ind Health 29(8):728-736' which also used a single dose of toluene. It should be noted that I'm not arguing for their removal from the report."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the animal species is appropriate for the most significant toxicological endpoint of the study, the Reviewer commented: "In my opinion, the animal species, mammals, particularly mice, rats, and monkeys were appropriate for the most significant toxicological endpoint which I believe to be dysfunction of the central nervous system."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the conclusions drawn by the authors of the animal studies are appropriate and accurately reflected in the text, the Reviewer commented: "With only a couple of exceptions mentioned below, I believe that the conclusions drawn by the authors of the studies appear to be appropriate and are accurately reflected in the text. However, on page 78, line 15, the wrong citation is used. Paez-Martinez et al. 2008 conducted a hot plate test, not exploratory behavior. The reference should be Paez-Martinez et al. 2003 which conducted the defensive burying task. On the bottom of page 78 (line 32-33) and top of page 79 (line 1-2) it is reported that Paez-Martinez et al. 2008 found that toluene ***increased*** anxiety-like behavior. First, the wrong citation is used. Paez-Martinez et al. 2008 conducted a hot plate test (pain test), not exploratory behavior. The reference should be Paez-Martinez et al. 2003 which conducted the defensive burying task. Second, this study actually demonstrated the opposite effect or a ***decrease*** in anxiety-like behavior."

RESPONSE: *ATSDR appreciates the identification of this error. It has been corrected.*

COMMENT: Regarding the question of whether all appropriate NOAELs and LOAELs are identified for each animal study and whether all appropriate toxicological effects are identified for the studies, the Reviewer commented: "In my opinion, all appropriate NOAELs and LOAELs were identified (not possible in a number of studies because of incomplete or conflicting results)."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is a discussion of the toxicities of the various forms of the substance, the Reviewer commented: "This is not applicable to toluene."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether appropriate statistical tests are used in the interpretation of the animal studies, the Reviewer commented: "As I mentioned previously, this is a difficult question to answer without going back through and reading all of the studies cited, several of which I don't have access. Although not a perfect system, one would hope that as peer-reviewed publications, reviewers of these articles would have checked to make sure that the proper statistical tests had been used. For the studies that I was able to review, it appears as though the appropriate statistical tests were used."
RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer is aware of other animal studies which may be important in evaluating the toxicity of the substance, the Reviewer had several suggestions:

SUGGESTION: On page 78, line 10 the authors should consider adding the following reference which demonstrated baseline differences in acute sensitivity and differential shifts in sensitivity after repeated exposures among inbred mouse strains suggesting a genetic basis for the behavioral effects to toluene (findings which support the statement, "A susceptible population will exhibit a different or enhanced response to toluene than will most persons exposed to the same level of toluene in the environment" on page 184.) :

Bowen, S.E., Kimar, S., and Irtenkauf, S. (2010). Comparison of toluene-induced locomotor activity in Four Mouse Strains. Pharmacology, Biochemistry, and Behavior, 95, 249-257. PMID: 20138905, http://doi:10.1016/j.pbb.2010.01.014.

RESPONSE: *The suggested reference was reviewed and added to Section 3.2.1.4.4, Animal Studies (p. 78) and the LSE table. It was also added to the discussion of susceptible populations in Section 3.10, Populations that are Unusually Susceptible (pp.185-186). (See page 137 of draft 4).*

SUGGESTION: On page 78, line 15, the authors should also consider adding Bowen et al 1996 which demonstrated similar anti-anxiety effects in an elevated plus-maze task:

Bowen, S.E., Wiley, J.L. & Balster, R.L. (1996). The effects of abused inhalants on mouse behavior in an elevated plus-maze. European Journal of Pharmacology, 312, 131-136. doi:10.1016/0014-2999(96)00459-1.

RESPONSE: *The suggested reference was reviewed and added to Chapter 3 (pg 79) and the LSE table.*

Profile Manager

The response here is incorrect, because the reference that was added on page #137 Section 3.2.1.4.4 reads "Bowen and Balster 1998, NOT Bowen and Balster 1996 as suggested by the reviewer.

SUGGESTION: On the bottom of page 78 (line 32-33) and top of page 79 (line 1-2) it is reported that toluene increased anxiety but this study demonstrated a ***decrease*** in anxiety-like behavior in unconditioned animals (had no effect on conditioned animals). Also, the wrong citation is used. Paez-Martinez et al. 2008 conducted a hot plate test, not exploratory behavior. The reference should be Paez-Martinez et al. 2003 which conducted the defensive burying task. This should also be changed on page 70 of the supplemental document. If the authors decide to keep this anti-anxiety reference (which I think they should as this is one of the reasons postulated for abusing toluene), I would also recommend adding Bowen et al 1996 which demonstrated similar anti-anxiety effects of toluene in an elevated plus-maze task:

Bowen, S.E., Wiley, J.L. & Balster, R.L. (1996). The effects of abused inhalants on mouse behavior in an elevated plus-maze. European Journal of Pharmacology, 312, 131-136. doi:10.1016/0014-2999(96)00459-1.

RESPONSE: *The citation error and error regarding the anxiolytic effects of toluene in the Paez-Martinez et al. (2003) study have been corrected. As indicated in the previous comment, the suggested reference was reviewed and added to Chapter 3 and the LSE table.*

SUGGESTION: On page 85, lines 24-26 consider adding

Apawu, A., Mathews, Tiffany, and Bowen, S.E. (In Press). Striatal Dopamine Dynamics in Mice Following Acute and Repeated toluene exposure. Psychopharmacology. http://link.springer.com/article/10.1007%2Fs00213-014-3651-x.

RESPONSE: *As suggested, this reference was reviewed and added to Section 3.2.1.4.5, Animal Studies Modeling High-Concentration Solvent Abuse and Section 3.5.2, Mechanisms of Toxicity.*

SUGGESTION: On page 199, lines 31-32 consider adding

Batis, J.C., Hannigan, J.H., and **Bowen, S.E.** (2010). Differential effects of inhaled toluene on locomotor activity in adolescent and adult rats. Pharmacology, Biochemistry, and Behavior, 96, 438-448. PMID: 20624418, http://dx.doi.org/10.1016/j.pbb.2010.07.003.

RESPONSE: *The suggested reference was reviewed and added to Section 3.2.1.4.5, Animal Studies Modeling High-Concentration Solvent Abuse; Section 3.7, Children's Susceptibility (pp. 174-176); and Section 3.12.2, Identification of Data Needs (p. 199)*

Levels of Significant Exposure (LSE) Tables and Figures

COMMENT: Regarding the question of whether the LSE tables and figures are complete and self-explanatory, the Reviewer commented: "I found the LSE tables and figures to be complete and self-explanatory. The "Users Guide" is sufficient for using the tables and figures. I didn't find any exposure level errors in going through the tables/figures with the exception on page 70 of the supplementary where "increased anxiety" should be "decreased anxiety." I have no other suggestions for improving the effectiveness of the LSE tables or figures."

RESPONSE: *The error on page 70 of the supplementary document has been corrected.*

COMMENT: Regarding the question of whether the Reviewer agrees with the categorization of "less serious" and "serious" effects cited in the LSE tables, the Reviewer commented: "I agree with the categorizations of "less serious" and "serious" for the effects cited in the LSE tables."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the MRLs are justifiable and if no MRLs were derived, do the data support deriving MRLs, the Reviewer commented: "In my opinion, the MRLs presented in the report are justifiable."

RESPONSE: *No revisions were suggested.*

Evaluation of Text

COMMENT: Regarding the question of whether the major limitations of the studies have been adequately and accurately discussed, the Reviewer commented: "I believe that the major limitations of the studies have been adequately and accurately discussed. I would suggest changing the discussion on the bottom of page 78 (line 32-33) and top of page 79 (line 1-2) where it is reported that toluene increased anxiety but this study demonstrated a ***decrease*** in anxiety-like behavior in unconditioned animals (had no effect on conditioned animals). In this study, several groups of mice were exposed to various solvents for 30-min exposures at which point these animals were tested either in an anxiety paradigm conditioned defensive burying (CDB) test or in a hot plate test. From the abstract of that paper, "All solvents but flurothyl produced anxiolytic-like actions being the order of potency toluene>benzene>TCE>diethyl ether." Also, the wrong citation is used. Paez-Martinez et al. 2008 did not use exploratory behavior. The reference should be Paez-Martinez et al. 2003 which conducted the defensive burying task."

RESPONSE: *The citation error and error regarding the anxiolytic effects of toluene in the Paez-Martinez et al. (2003) study have been corrected.*

COMMENT: Regarding the question of whether the effect or key endpoint has been critically evaluated for its relevance in both humans and animals, the Reviewer commented: "Yes, I believe that the key "endpoints" have all been critically evaluated for both humans and animals."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether "bottom-line" statements have been made regarding the relevance of the endpoint for human health, the Reviewer commented: "Yes, I believe these statements have been made."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the conclusions are appropriate given the overall database, the Reviewer commented: "Yes, I believe that the conclusions are evidenced based and appropriate given the available databases."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether adequate attention has been paid to dose-response relationships for both human and animal data, the Reviewer commented: "I believe that adequate attention has been paid to dose-response relationships for both human and animal data. The report provides a detailed knowledge of a number of dose–response relationships (acute, intermediate, and chronic) more so in animals than humans, in relation to all sources of exposure (oral, inhalation, dermal), the types of toxic effect elicited by toluene alone and in combination with other chemicals/drugs, as well as providing "thresholds" for specified toxic effects. Variations in sensitive groups within the population is also discussed."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the animal data has been used to draw support for any known human effects, the Reviewer commented: "Yes, animal data has been used to draw support for several toluene effects in humans including alteration/dysfunction of the central nervous system, alterations in heart rhythms, as well as skin and eye irritation. Humans who have abused solvents and have repeatedly inhaled toluene at high exposure levels (4,000–12,000 ppm) have demonstrated degenerative changes in white matter regions of the brain which have been linked with severe neurological impairments. In addition, human studies of occupationally exposed workers suggest that long term exposure to lower exposures of toluene (<200 ppm) can produce subtle changes in neurological functions including cognitive and neuromuscular performance, hearing, and color discrimination. There are a number of adequately designed animal studies (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels) that have consistently reported neurological alterations following acute, intermediate, and chronic inhalation exposure to toluene including ataxia, tremors, and difficultly in walking, symptoms that are also observed in humans.

RESPONSE: *No revisions were suggested.*

Section 3.4. TOXICOKINETICS

COMMENT: Regarding the question of whether there is an adequate discussion of absorption, distribution, metabolism, and excretion of the substances, the Reviewer commented: "I believe that there is excellent discussion of the absorption, distribution, metabolism, and excretion of toluene. I have no other suggestions."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the major organs, tissues, etc in which the substance is stored have been identified, the Reviewer commented: "Toluene that has been absorbed into the body is known to be distributed widely to tissues throughout the body including adipose tissue, brain, bone marrow, liver, and kidney. This has been clearly identified and discussed in the text."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether all applicable metabolic parameters have been presented and all available PB/PK models have been presented, the Reviewer commented: "Yes, I believe all applicable metabolic parameters as well as pharmacokinetic/pharmacodynamic models have been presented."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is adequate discussion of the differences in toxicokinetics between animals and humans, the Reviewer commented: "Yes, in my opinion, there is adequate discussion of the differences in toxicokinetics between humans and animals."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is an adequate discussion of the relevance of animal toxicokinetic information for humans, the Reviewer commented: "Yes, in my opinion, there is adequate discussion of the relevance of animal toxicokinetic information for humans."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is a discussion of the toxicokinetics of different forms of the substance, the Reviewer commented: "This is not applicable to toluene."

RESPONSE: *No revisions were suggested.*

Section 3.5. MECHANISMS OF ACTION

COMMENT: Regarding the question of whether all possible mechanisms of action have been discussed, the Reviewer commented: "I believe all possible mechanisms of action have been discussed."

RESPONSE: *No revisions were suggested.*

Section 3.8. BIOMARKERS OF EXPOSURE AND EFFECT

COMMENT: Regarding the question of whether all the biomarkers of exposure are specific for the substance or are general for a class of substances, the Reviewer commented: "The biomarkers used to identify or quantify exposure to toluene that are specific to toluene are ortho-cresol and unchanged toluene levels in urine as well as toluene levels in blood. Arguments were given against using hippuric acid in urine (byproduct of toluene) because background urinary hippuric acid from consumption of benzoate in foods and beverages is expected to mask contributions from workplace exposure to toluene."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are valid tests to measure the biomarkers of exposure, the Reviewer commented: "Yes, there are valid tests to measure the biomarker of exposure"

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are valid tests to measure the biomarkers of effect, the Reviewer commented: "There are no specific biomarkers used to characterize the effects from toluene exposure. While inhalant/toluene abusers can have MRI techniques used to detect changes in the brain (in combination with evidence of an exposure history), this is not a practical approach for assessing the effects of short- or long-term exposures to low-level exposures of toluene which are typical for environmental releases. This is consistent with other sections of the text."

RESPONSE: *No revisions were suggested.*

Section 3.9. INTERACTIONS WITH OTHER CHEMICALS

COMMENT: Regarding the question of whether there is an adequate discussion of the interactive effects with other substances, the Reviewer commented: "Yes, I believe that there is adequate discussion of the interactive effects with other substances (phenobarbital, ethanol, benzene, xylene, n-hexane, haloperidol, etc.). The interactions and concerns of workers exposed to toluene and these other substances was discussed."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text discusses the mechanisms of interactions with other substances, the Reviewer commented: "Yes, the mechanisms of these interactions were discussed in detail."

RESPONSE: *No revisions were suggested.*

Section 3.10. POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

COMMENT: Regarding the question of whether there is a discussion of populations at higher risk because of biological differences which make them more susceptible, the Reviewer commented: "Yes, there is a detailed discussion of populations at higher risk because of biological differences which make them more susceptible. In particular, ethnic populations with differences in the relative efficiency of their enzymes (CYP isozymes, alcohol dehydrogenase, and aldehyde dehydrogenase) may lead to differences in toluene susceptibility. I agree with the choices of populations. The authors should consider adding the following reference which demonstrated baseline differences in acute sensitivity and differential shifts in sensitivity after repeated exposures among inbred mouse strains suggesting a genetic basis for the behavioral effects to toluene (findings which support the statement, "A susceptible population will exhibit a different or enhanced response to toluene than will most persons exposed to the same level of toluene in the environment" on page 184. :

Bowen, S.E., Kimar, S., and Irtenkauf, S. (2010). Comparison of toluene-induced locomotor activity in Four Mouse Strains. Pharmacology, Biochemistry, and Behavior, 95, 249-257. PMID: 20138905, http://doi:10.1016/j.pbb.2010.01.014

RESPONSE: *The provided study was reviewed added to the discussion of susceptible populations in Section 3.10, Populations that are Unusually Susceptible (pp.185-186).*

Section 3.11. METHODS FOR REDUCING TOXIC EFFECTS

COMMENT: Regarding the question of whether the management and treatment discussed in Section 3.11 is specific for the substance or is general for a class of substances, the Reviewer commented: "Management and treatment for toluene is similar to that of other volatile substances. Physical activity is contraindicated (increases absorption of toluene) as is emesis following oral exposure due to the possibility of aspiration of stomach contents. There appears to be no effective way to reduce peak absorption following inhalation exposure and the use of activated charcoal and lavage is proposed to help to reduce oral exposure. Rapid rinsing of the skin with water or washing with soap and water may reduce the opportunity for dermal absorption. If eye exposure occurs, rinsing of the eyes is recommended. Oxygen therapy and an increase of fluids consumed are also recommended, especially in cases of toluene abuse."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is any controversy associated with the treatment and whether it is well accepted, the Reviewer commented: "I don't believe that there is any controversy with the treatments proposed as these are well established procedures for many substances."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are any hazards associated with the treatment of populations that are unusually susceptible to the substances, the Reviewer commented: "The current information suggests that toluene metabolism may be lower in developing fetuses and children at very early stages of development which may make them more susceptible to toluene toxicity."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there are treatments available to prevent the specific substance from reaching the target organ, the Reviewer commented: "Oxygen therapy and an increase of fluids consumed are recommended, especially in cases of toluene abuse."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether there is any controversy associated with the treatment for preventing the substance from reaching the target organ, the Reviewer commented: "I don't believe that there is any controversy associated with the treatments presented. Unfortunately, there appears to be a lack of information available on methods of mitigating the toxic effects of toluene."

RESPONSE: *No revisions were suggested.*

Section 3.12. ADEQUACY OF THE DATABASE

COMMENT: Regarding the question of whether the Reviewer knew of other studies which may fill a data gap, the Reviewer commented: "I am not aware of any other studies that could currently fill the data gaps."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the data needs are presented in a neutral, non-judgmental fashion, the Reviewer commented: "I agree that the data is presented in a neutral, non-judgmental fashion."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the Reviewer agrees with the identified data needs, the Reviewer commented: "I agree with the identified data needs."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text indicates whether any information on the data need exists, the Reviewer commented: "Yes, the text indicates the need for additional data. For example, while there is limited data for the dermal, this is not the primary routes of human exposure. It is also pointed out that the database is also lacking studies on intermediate-duration exposure in humans. Additionally, the lack of intermediate-duration studies designed to assess neurobehavioral alterations and/or mechanisms of neurotoxicity following oral exposure could be useful in evaluating human health risk. The chronic effects of toluene have also not been investigated in humans or animals following oral or dermal exposures, and the carcinogenic potential has not been studied following dermal exposure."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text adequately justifies why further development of the data needs would be desirable or justifies the inappropriateness of developing the data need at present, the Reviewer commented: "Yes. For example, it is clear that no-effect levels for intermediate and low-level inhalation exposure in air have not been thoroughly investigated. Determining these values would aid in evaluating the human health risk, and could potentially be used to derive an intermediate-duration MRL for inhalation exposures."

RESPONSE: *No revisions were suggested.*

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

COMMENT: Regarding the question of whether the Reviewer is aware of any chemical and physical property information or values that are wrong or missing, the Reviewer commented: "I am not aware of any information that may be wrong or missing from the chemical and physical properties tables."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether information was provided on the various forms of the substance, the Reviewer commented: "Not applicable"

RESPONSE: *No revisions were suggested.*

CHAPTER 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

COMMENT: Regarding the question of whether the Reviewer is aware of any information on the production, import/export, use or disposal of the substance that is wrong or missing, the Reviewer commented: "I am not aware of any information that may be wrong or missing"

RESPONSE: *No revisions were suggested.*

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

COMMENT: Regarding the question of whether the text appropriately traces the substance from its point of release to the environment until it reaches the receptor population, the Reviewer commented: "Yes, I believe that the text appropriately traces toluene from its point of release to the environment until it reaches the receptor population. I also believe that the text provides sufficient and technically sound information regarding the extent of occurrence at NPL sites. I'm not aware of any other relevant information."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text covers pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media, the Reviewer commented: "Yes, the text covers pertinent information relative to transport, partitioning, transformation, and degradation of toluene in all media."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text provides information on levels monitored or estimated in the environment (including background levels), that proper units are used for each medium, and that the information includes the form of the substance measured, the Reviewer commented: "Yes, the text provides information on toluene levels monitored or estimated in the environment, including background levels. Proper units are used for each medium and there is an appropriate discussion of the quality of the information."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the text describes sources and pathways of exposure for the general population, occupations involved in the handling of the substance, and populations with potentially high exposures, the Reviewer commented: "Yes, the text describe sources and pathways of toluene exposure for the general population and occupations involved in the handling of toluene, as well as populations with potentially high exposures (gasoline service stations, commercial painters, printers, etc.)."

RESPONSE: *No revisions were suggested.*

CHAPTER 7. ANALYTICAL METHODS

COMMENT: Regarding the question of whether the Reviewer is aware of additional methods that should be added to the profile, the Reviewer commented: "I'm not aware of any additional methods that can be added to the tables."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether the methods have been included for measuring key metabolites previously mentioned in the text, the Reviewer commented: "Yes, methods have been included in the text for measuring key metabolites of toluene."

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the question of whether unique issues related to sampling for the substance exist and have been adequately addressed in the text, the Reviewer commented: "I don't believe that this is applicable to toluene as a variety of analytical methods exist for sampling toluene."

RESPONSE: *No revisions were suggested.*

CHAPTER 8. REGULATIONS AND ADVISORIES

COMMENT: Regarding the question of whether the Reviewer is aware of other regulations or guidelines that may be appropriate for Table 8-1, the Reviewer commented: "I'm not aware of any other regulations or guidelines."

RESPONSE: *No revisions were suggested.*

CHAPTER 9. REFERENCES

COMMENT: Regarding the question of whether there are additional references that provide new data or if there are better studies than those already in the text, the Reviewer commented: "I have suggested the possibility of additional references in previous sections and will not duplicate that here."

RESPONSE: *Responses regarding additional references can be found in previous sections.*

UNPUBLISHED STUDIES (IF APPLICABLE TO REVIEW)

COMMENT: Regarding the questions on unpublished studies, the Reviewer commented: "I'm not aware of any unpublished studies that should be included."

RESPONSE: *No revisions were suggested.*