DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR DEET (N,N-DIETHYL-META-TOLUAMIDE)

Prepared by:

SRC, Inc.
7502 Round Pound Road
North Syracuse, NY 13212

Prepared for:

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

December 2014

Peer reviewers for the third pre-public comment draft of the Toxicological Profile for DEET were:

Mohamed B. Abou-Donia, Ph.D.
Professor of Pharmacology and Cancer Biology
And of Neurobiology
Duke University Medical Caner
Durham, North Carolina 27710

Thomas G. Osimitz, Ph.D.
Diplomate, American Board of Toxicology
European Registered Toxicologist
Science Strategies, LLC
1001 East Market Street, Suite 202
Charlottesville, VA 22902

Andrey I. Nikiforov, Ph.D.
President, Principal
2365 Hunters Way
Charlottesville, VA 22911

Comments provided by Peer Reviewer #1:

Charge Questions and Responses

GENERAL

COMMENT: Charge question: *Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be?* The Reviewer commented: "No."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Are there any general issues relevant to child health that have not been discussed in the profile and should be?* The Reviewer commented: "No."

RESPONSE: *No response necessary.*

CHAPTER 1

COMMENT: Charge question: *Does the chapter present the important information in a non-technical style suitable for the average citizen?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *In your opinion, do the answers to the questions adequately address the concerns of the lay public?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Are these summary statements consistent, and are they supported by the technical discussion in the remainder of the text? Please note sections that are weak and suggest ways to improve them.* The Reviewer commented: "I have suggested some clarifying language in the document with tracked changes."

RESPONSE: *All editorial changes suggested by the Reviewer were done.*

COMMENT: Charge question: *Are scientific terms used that are too technical or that require additional explanation?* The Reviewer commented: "No."

RESPONSE: *No response necessary.*

CHAPTER 2

COMMENT: Charge question: *Do you agree with those effects known to occur in humans as reported in the text?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Are the effects only observed in animals likely to be of concern to humans? Why or why not?* The Reviewer commented: "We have reasons to suspect qualitative species differences, but it is important to note that the animal effects occur often only at lethal or near lethal levels. More important, we have 50 years of experience of extensive, intentional exposure to humans to evaluate."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Have exposure conditions been adequately described?* The Reviewer commented: "Ok as far as it goes. I assume that the intent is not to quantify intentional exposures. Estimates are also available in documents from CalEPA, USEPA, and Health Canada."

RESPONSE: *No response necessary.*

CHAPTER 3

Section 3.2

Toxicity – Quality of Human Studies

COMMENT: Charge question: *Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? If not, were the major limitations of the studies sufficiently described in the text without providing detailed discussions?* The Reviewer commented: "With respect to the often-cited NIOSH study (1986), it should be noted that exposure was inferred from only survey responses, a notable weakness. Not actual quantification was possible. Also, can you provide some perspective on isolated or sporadic reports? I am not sure what to suggest, but consider:

> "The only relevant information is that from a report by Clem et al. (1993), which states that a 61-year-old woman developed nausea, vomiting, and explosive diarrhea after spraying herself with a DEET-containing insect repellent."

This is most likely coincidental. Leaving it without comment seems to ascribe more significance to it than it deserves.

With regard to 3.2.3.4, it is worth mentioning that causality is difficult to establish here (all of these cases). Please see Osimitz and Murphy for an attempt to do so for some of the cases."

RESPONSE: *A statement was added in Section 2.2, SUMMARY OF HEALTH EFFECTS, indicating that because exposure was assessed through a survey, the findings of the NIOSH (1986) report should be interpreted with caution. This was also added the first time the NIOSH report is cited in Section 3.2 (under Respiratory Effects). A statement was also added to the paragraph where the gastrointestinal effects in the 61-year-old woman are mentioned indicating that the possibility that the effects were coincidental could not be ruled out. In addition, a sentence was added at the beginning of Section 2.2 stating that considering the many millions of applications of DEET per year in the United States, it is difficult to definitively link reported signs and symptoms to DEET use. This is cited to Osimitz et al.*

(2010) and should apply to all the effects associated with exposure to repellents containing DEET, not only to the cases describing neurological effects summarized in Section 3.2.3.4.

COMMENT: Charge question: *Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the profile? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)?* The Reviewer commented: "Yes, keeping the comments above in mind."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Were all appropriate NOAELs and/or LOAELs identified for each study? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations?* The Reviewer commented: "Not relevant for most of the human data."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Were the appropriate statistical tests used in the studies? Would other statistical tests have been more appropriate? Were statistical test results of study data evaluated properly?* The Reviewer commented: "Most of the human data do lend themselves to statistical analysis. No further comments."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Are you aware of other studies which may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.* The Reviewer commented: "I have cited a recent case of ingestion of DEET (Wiles et al., J. Anal. Toxicol.1-3, 2014). This should be included in the discussion about human effects following ingestion."

RESPONSE: *Relevant information from the Wiles et al. (2014) study was added to the appropriate sections of the profile.*

Toxicity – Quality of Animal Studies

COMMENT: Charge question: *Were adequately designed animal studies identified in the text (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)?* The Reviewer commented: "Generally, good. I appreciate that you often pointed out deficiencies in the studies when present and were careful not to use deficient studies in an attempt to derive MRLs."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the text? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)?* The Reviewer commented: "Overall, fine. I made some comments about the limitations of the often-cited NIOSH (1986) survey."

RESPONSE: *As previously mentioned, statements were added to the profile indicating that the findings from the NIOSH (1986) report should be interpreted with caution.*

COMMENT: Charge question: *Were all appropriate NOAELs and LOAELs identified for each study? Were all appropriate toxicological effects identified for the studies?* The Reviewer commented: "OK, overall. I recommend consistently indicating if a NOAEL is the highest dose tested in the study. It is important to know this."

RESPONSE: *The Reviewer's recommendation is followed throughout the profile.*

COMMENT: Charge question: *If appropriate, is there a discussion of the toxicities of the various forms of the substance?* The Reviewer commented: "Not applicable."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Were the appropriate statistical tests used in the interpretation of the studies? If not, which statistical test would have been more appropriate? Were statistical test results of study data evaluated properly?* The Reviewer commented: "Seems fine."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Are you aware of other studies which may be important in evaluating the toxicity of the substance?* The Reviewer commented: "None, other than the paper cited above."

RESPONSE: *Information from the cited paper (Wiles et al. 2014) was added to the profile.*

Levels of Significant Exposure (LSE) Tables and Figures

COMMENT: Charge question: *Are the LSE tables and figures complete and self-explanatory? Does the "Users Guide" explain clearly how to use them? Are exposure levels (units and dose) accurately presented for the route of exposure?* The Reviewer commented: "Generally okay."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?* The Reviewer commented: "Yes, very well thought out. But in some cases '>10% reduced terminal body weight' is considered a less serious effect. Do we not have the exact decrease? I say this because in other cases a '22% body weight loss' is considered a serious effect."

RESPONSE: *Some studies present the data only graphically such that only an estimate of the body weight can be made. Three such cases appear in Table 3-1. Weight loss or decreases in body weight of 20% or greater are classified as serious LOAELs, which is the proper classification for 22% body weight loss.*

COMMENT: Charge question: *If MRLs have been derived, are the values justifiable? If no MRLs have been derived, do you agree that the data do not support such a derivation?* The Reviewer commented: "Yes for intermediate term exposures. But:

> "Intermediate-duration oral MRL is protective for chronic-duration exposure.
> The available chronic-duration oral database does not support derivation of a chronic-duration oral MRL for DEET. However, long-term exposure does not lead to more toxic effects than those reported for intermediate-duration exposure, so the intermediate-duration oral MRL of 1 mg/kg/day for DEET is protective for chronic-duration exposure."

In essence, isn't 1 mg/kg/day then a chronic-duration oral MRL?"

RESPONSE: *No, because the chronic-duration data were inadequate (no toxicologically-significant LOAEL was identified) for MRL derivation. Because the intermediate-duration LOAEL of 250 mg/kg/day is lower than chronic-duration LOAELs, the intermediate-duration oral MRL, which is based on a NOAEL of 100 mg/kg/day, is protective for chronic exposures.*

Evaluation of Text

COMMENT: Charge question: *Have the major limitations of the studies been adequately and accurately discussed? How might discussion be changed to improve or more accurately reflect the proper interpretation of the studies?* The Reviewer commented: "Generally, yes. Please see document for specific comments."

RESPONSE: *Text suggested by the Reviewer was added in the sections indicated.*

COMMENT: Charge question: *Has the effect, or key endpoint, been critically evaluated for its relevance in both humans and animals?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Have "bottom-line" statements been made regarding the relevance of the endpoint for human health?* The Reviewer commented: "I don't see this in the document."

RESPONSE: *In the case of DEET, for which neurological effects are the main effects, it seems unnecessary to indicate whether or not a specific end point is relevant for human health. A statement was added in Section 2.2, SUMMARY OF HEALTH EFFECTS, indicating that neurological effects observed in animals exposed to high amounts of DEET support the findings in humans exposed to high amounts of DEET.*

COMMENT: Charge question: *Are the conclusions appropriate given the overall database?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.* The Reviewer commented: "Yes, but as pointed out in the text, quantitative human exposure data are very limited and unreliable (e.g., based on surveys, etc. as with NIOSH 1986)."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Has the animal data been used to draw support for any known human effects?* The Reviewer commented: "The discussion with respect to neurotoxicity is adequate."

RESPONSE: *No response necessary.*

SECTION 3.4 TOXICOKINETICS

COMMENT: Charge question: *Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Have the major organs, tissues, etc. in which the substance is stored been identified?* The Reviewer commented: "No comment was provided."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Have all applicable metabolic parameters been presented? Have all available pharmacokinetic/pharmacodynamics models and supporting data been presented?* No comment was provided by the Reviewer.

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Is there adequate discussion of the differences in toxicokinetics between humans and animals? What other observations should be made?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Is there an adequate discussion of the relevance of animal toxicokinetic information to humans?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *If applicable, is there a discussion of the toxicokinetics of different forms of the substance (e.g., inorganic vs. organic mercury)?* The Reviewer commented: "Not applicable."

RESPONSE: *No response necessary.*

Section 3.5

COMMENT: Charge question: *The purpose of this section is to provide a brief overview of known mechanisms of metabolism, absorption, distribution, and excretion, and then a discussion of any substance reactions or physiological processes that may affect these mechanisms. Have all possible mechanisms of action been discussed?* The Reviewer commented: "Yes, although there is limited knowledge here. Also, DEET doesn't have an obvious specific target site."

RESPONSE: *No response necessary.*

Section 3.8

COMMENT: Charge question: *Are the biomarkers of exposure specific for the substance or are they for a class of substances?* The Reviewer commented: "There are no appropriate biomarkers at present."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Are there valid tests to measure the biomarker of exposure? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.* The Reviewer commented: "There are no appropriate biomarkers."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Are the biomarkers of effect specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?* The Reviewer commented: "There are no appropriate biomarkers."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Are there valid tests to measure the biomarker of effect? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.* The Reviewer commented: "There are no appropriate biomarkers."

RESPONSE: *No response necessary.*

Section 3.9

COMMENT: Charge question: *Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? If not, please clarify and add additional references.* The Reviewer commented: "Yes, but it is important to note that most of the studies reported were aimed at understanding potential interaction associated with Gulf War Syndrome. It would be good to discuss the relevance (or lack thereof) of these studies to civilian exposures to DEET and other chemicals."

RESPONSE: *A paragraph stating the lack of relevance of these studies to civilian exposed to DEET and other chemicals was added at the end of Section 3.9.*

COMMENT: Charge question: *Does the discussion concentrate on those effects that might occur at hazardous waste sites? If not, clarify and add additional references.* The Reviewer commented: "None of the chemical studied (e.g., permethrin, pyridostigmine bromide) are likely to be encountered at waste sites."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? If not, please clarify and provide any appropriate references.* The Reviewer commented: "No others known."

RESPONSE: *No response necessary.*

Section 3.10

COMMENT: Charge question: *Is there a discussion of populations at higher risk because of biological differences which make them more susceptible? Do you agree with the choices of populations? Why or why not? Are you aware of additional studies in this area?* The Reviewer commented: "Yes, but none have been identified."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Do you agree with the choices of populations?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Are you aware of additional studies in this area?* The Reviewer commented: "No."

RESPONSE: *No response necessary.*

SECTION 3.11

General Discussion Regarding Treatments to Reduce Peak Absorption

COMMENT: Charge question: *Is the management and treatment specific for the substance, or is it general for a class of substances?* The Reviewer did not provide any comments.

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Is there any controversy associated with the treatment? Is it a "well accepted" treatment?* The Reviewer did not provide any comments.

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?* The Reviewer did not provide any comments.

RESPONSE: No response necessary.

Methods to Enhance Elimination of the Absorbed Dose or Body Burden

COMMENT: Charge question: *Are treatments available to prevent the specific substance from reaching the target organ(s), or are the actions general for a class of substances?* The Reviewer commented: "No."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Is there any controversy associated with the treatment? Is it a "well accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method?* The Reviewer commented: "Not applicable."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?* The Reviewer commented: "Not applicable."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Are there any treatments to prevent adverse effects as the substance is being eliminated from the major organs/tissues where it has been stored (e.g., as a substance is eliminated from adipose tissue, can we prevent adverse effects ring in the target organ)?* The Reviewer commented: "No, not relevant for DEET."

RESPONSE: *No response necessary.*

Methods to Block the Mechanisms of Toxic Action

COMMENT: Charge question: *Are there treatments available to prevent the specific substance from reaching the target organ(s), or are the actions general for a class of substances?* The Reviewer commented: "No."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Is there any controversy associated with the treatment? Is it a "well accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method?* The Reviewer commented: "Not applicable."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?* The Reviewer commented: "Not applicable."

RESPONSE: *No response necessary.*

Section 3.12

Existing Information on Health Effects

COMMENT: Charge question: *Do you know of other studies that may fill a data gap? If so, please provide the reference.* The Reviewer commented: "Mentioned above."

RESPONSE: *Data from Wiles et al. (2014) were added to the profile.*

Identification of Data Needs

COMMENT: Charge question: *Are the data needs presented in a neutral, non-judgemental fashion? Please note where the text shows bias.* The Reviewer commented: "Please see text."

RESPONSE: *No response required here.*

COMMENT: Charge question: *Do you agree with the identified data needs? If not, please explain your response and support your conclusions with appropriate references.* The Reviewer commented: "Please see text."

RESPONSE: *No response required here.*

COMMENT: Charge question: *Does the text indicate whether any information on the data need exists?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Does the text adequately justify why further development of the data need would be desirable; or conversely, justify the "inappropriateness" of developing the data need at present? If not, how can this justification be improved.* The Reviewer did not provide any comments.

RESPONSE: *No response necessary.*

CHAPTER 4

COMMENT: Charge question: *Are you aware of any information or values that are wrong or missing in the chemical and physical properties tables?* No changes were recommended.

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Is information provided on the various forms of the substance?* The Reviewer commented: "Not applicable."

RESPONSE: *No response necessary.*

CHAPTER 5

COMMENT: Charge question: *Are you aware of any information that is wrong or missing?* The Reviewer commented: "No."

RESPONSE: *No response necessary.*

CHAPTER 6

COMMENT: Charge question: *Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information?* The Reviewer commented: "Very limited. It would be good to how for how many sites was DEET actually analyzed."

RESPONSE: *NPL site information is limited and the HazData database is no longer updated (as of 2008); the actual number of sites tested for DEET specifically is not readily available.*

COMMENT: Charge question: *Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Does the text provide information on levels monitored or estimated in the environment, including background levels?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Are proper units used for each medium?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Does the information include the form of the substance measured?* The Reviewer commented: "Not applicable."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Is there an adequate discussion of the quality of the information?* The Reviewer commented: "Limited."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Do you know of other relevant information?* The Reviewer commented: "No."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Does the text describe 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 Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Do you agree with the selection of these populations?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

CHAPTER 7

COMMENT: Charge question: *Are you aware of additional methods that can be added to the tables? If so, please provide copies of appropriate references.* The Reviewer commented: "No."

RESPONSE: *No response necessary.*

COMMENT: Charge question: *Have methods been included for measuring key metabolites mentioned previously in the text?* The Reviewer commented: "Yes."

RESPONSE: *No response necessary.*

CHAPTER 8

COMMENT: Charge question: *Are you aware of other regulations and guidelines that may be appropriate for the table?* The Reviewer commented: "None, except the citation I added in the text about proper intended use of DEET by the American Academy of Pediatrics."

RESPONSE: *The recommendations of the American Academy of Pediatrics have been added to Section 6.6, EXPOSURES OF CHILDREN, along with guidelines and recommendations from EPA and CDC.*

CHAPTER 9

COMMENT: Charge question: *Are there additional references that provide new data or are there better studies than those already in the text?* The Reviewer commented: "None."

RESPONSE: *No response necessary.*

RESPONSE TO COMMENTS THAT APPEAR IN THE ANNOTATED PAGES

COMMENT: Under the heading, How DEET Enters your Body, the Reviewer suggests deleting the word *absorbed.*

RESPONSE: *The text was revised to "…in the air can be absorbed in your lungs after inhalation."*

COMMENT: Under the heading, How DEET Enters your Body, the Reviewer suggests deleting the word *into.*

RESPONSE: *The change was made as suggested.*

COMMENT: Under the heading, How DEET Enters your Body, the Reviewer comments: "Then it has not been "absorbed" into the lungs."

RESPONSE: *The text was revised; "…if it is not absorbed first".*

COMMENT: Regarding Section 2.1, the Reviewer suggests replacing "consumed as" with "use in"

RESPONSE: *The change was made as suggested.*

COMMENT: Regarding Section 2.1, the Reviewer comments that the words "individual products" replace "brands" and that a sentence be added from page 105.

RESPONSE: *The text was revised to: "Insect repellent products containing DEET range in concentration from 4 to 100%. As of November 2014, there were 29 companies in the United States that manufactured approximately 118 consumer products containing DEET (NPIRS 2014)."*

COMMENT: Regarding Section 2.1, the Reviewer suggests that the phrase "be of concern" be deleted.

RESPONSE: *The text was revised to: "Inhalation may be a source for exposure when aerosol formulations are used, albeit a minor route of exposure."*

COMMENT: Regarding Section 2.1, the Reviewer comments "Not sure how meaningful this is seeing that most of DEET is metabolized before being excreted."

RESPONSE: *Although it is metabolized, it seems relevant to include data on how much of the parent compound is present in the population. Clarification was added to the end of paragraph: "It should be noted, however, that human monitoring data measuring the parent compound DEET do not directly correlate to initial exposure concentrations due to the fact that the majority of absorbed DEET is metabolized."*

COMMENT: Regarding the following sentence: "The study authors attributed the low bioavailability in this study to the use of the ethanol vehicle which enhances evaporation," the Reviewer states: "Not sure that this is true. I don't understand how this could happen. Ethanol is also likely to enhance penetration."

RESPONSE: *Data were added from a study by Stinecipher and Shah (1997) that shows that ethanol at certain concentrations (30-45%) can enhance DEET penetration through preparations of human skin in vitro.*

COMMENT: The Reviewer questions: "Is there any way to indicate relative importance of the major pathways(s)?" The comment refers to the metabolic scheme for DEET.

RESPONSE: *The preferred pathway will be determined by the concentration of the corresponding CYPs and will vary between individuals, as the text indicates.*

COMMENT: The Reviewer comments: "Not sure what you would be looking for here. Conjugation and renal excretion?" The comment refers to the following sentence that appears in Section 3.5.1, Pharmacokinetic Mechanisms: "No information was located regarding mechanisms of elimination and excretion of parent compound or metabolites of DEET."

RESPONSE**:** *Issues to discuss include contribution of various routes (renal, pulmonary, biliary, other) to excretion of parent compound or metabolites. Are excretion mechanisms active or passive? Do they show capacity limitation, etc.?*

COMMENT: The Reviewer questions: "Isn't there already a good set of baseline studies? Specifically what more is needed and what would it provide?" The comment refers to the following text that appears at the end of Acute-Duration Exposure in Section 3.12.2, Identification of Data Needs: "Therefore, animal studies that examine a wide range of end points (systemic, immunological, neurological, reproductive, and developmental) and establish dose-response relationships would be valuable."

RESPONSE: *The acute-duration database is incomplete. As the text indicates, information on a number of end points is missing. Calling for studies here does not necessarily mean that studies will be conducted, but the issue will be evaluated.*

COMMENT: The Reviewer questions: "Are there any QSAR reasons to suspect geno or Cx?" The comment refers to the section on genotoxicity in the data needs. Specifically to the following sentences: "Evidence of DNA damage was reported in cultured primary human nasal mucosal cells (Tisch et al. 2002). Further studies in human cells would provide valuable information."

RESPONSE: *ATSDR is not aware of QSAR studies. At minimum, the findings from Tisch et al. (2002) need to be replicated. This was added to the text.*

COMMENT: The Reviewer comments: "Please see the DEET Registry publication." The comment refers to the following sentence: "Follow-up of the individuals with the most severe effects (i.e., seizures) would provide valuable information regarding possible long-term effects due to acute exposure."

RESPONSE: *It is difficult to determine exactly what the Reviewer is suggesting. Follow-up of patients is mentioned in Chapter 2 and is cited to Osimitz et al. (2010), which is a publication about the DEET Registry.*

COMMENT: The Reviewer notes: "This only captures government-sponsored work. I would recommend contacting the DEET Joint Venture, c/o Ms. Susan Little in Washington (slittle@cspa.org) to see if industry is contemplating any work." The comment refers to Section 3.12.3, Ongoing Studies, which states that no ongoing studies pertaining DEET were identified in RePorter (2014).

RESPONSE: *SRC, Inc. sent an e-mail to Ms. Little on 11/11/2014 asking if she provide information regarding the Reviewer's suggestion. No answer has been received as of 12/1/2014.*

COMMENT: In Section 4.1, the Reviewer suggests deleting the word "animal" and replacing it with "mammalian."

RESPONSE: *The change was made as suggested.*

COMMENT: In Section 4.1, the Reviewer suggests adding "(such as isopropanol and water)."

RESPONSE: *The sentence was revised to include "(such as ethanol, isopropanol, or water)."*

COMMENT: Regarding use data in Section 5.3, the Reviewer comments: "These data are 15 years old and conflict with other statements in this document."

RESPONSE: *The sentences in question were reworded and updated with data from NPIRS (2014).*

COMMENT: Regarding use data in Section 5.3, the Reviewer questions: "Is this relevant for this document?"

RESPONSE: *This statement provides supporting data on proposed additional uses; the sentence was revised to include the following text at the end of the sentence "...of some applications."*

COMMENT: Regarding use data in Section 5.3, the Reviewer notes: "This is confusing. Please select to most recent data and use this consistently."

RESPONSE: *Recent data are very limited. Data in this section are provided for supporting information.*

COMMENT: In Section 6.1, the Reviewer suggests replacing "dermal contact" with "intentional application to the skin of."

RESPONSE: *The change was made as suggested.*

COMMENT: In Section 6.2.2 regarding DEET releases to air, the Reviewer questions "Is there any reason to believe that these are significant sources?"

RESPONSE: The Reviewer is referring to boilerplate text containing the source that is used when there is no information in the TRI database for the chemical; the source has been updated to the more recent 2005 reference.

COMMENT: In Section 6.2.2 regarding DEET releases to air, the Reviewer suggests adding "Because of its limited absorption through human skin, t…"

RESPONSE: *The change was made as suggested.*

COMMENT: In Section 6.2.2 regarding DEET releases to air, the Reviewer suggests deleting the space in waste water.

RESPONSE: ATSDR guidance documents indicate a preference for waste water as two words.

COMMENT: In Section 6.2.3 regarding DEET releases to soil, the Reviewer questions "Is there any reason to believe that these are significant sources?"

RESPONSE: *The Reviewer is referring to boilerplate text containing the source that is used when there is no information in the TRI database for the chemical; the source has been updated to the more recent 2005 reference.*

COMMENT: The Reviewer questions the validity of the sentence "DEET was detected in marine coastal areas along the Florida Keys following an underwater music festival in which human recreational activities occurred in and around the water."

RESPONSE: *The data are accurate according the referenced source.*

COMMENT: In Section 6.5 regarding exposure of DEET to the general population, the Reviewer suggests rewording the sentence: "These values may underestimate actual exposure levels as it is probable that users may apply the product more than once per day" to "These values may underestimate actual exposure levels in some users as it is probable that some users may apply the product more than once per day."

RESPONSE: *The change was made as suggested.*

COMMENT: In Section 6.6 regarding exposure of DEET to children, the Reviewer states: "It is important to note that: 'The AAP recommends that repellents should contain no more than 30% DEET when used on children. Insect repellents also are not recommended for children younger than 2 months.' http://www.healthychildren.org/English/safetyprevention/ at-play/Pages/Insect-Repellents.aspx. It would be worth mentioning in all of the places that you talked about children's exposure."

RESPONSE: *The paragraph was edited to reflect EPA, CDC, and AAP recommendations for children: "A recent interim review of DEET by the EPA, under the Registration Review Program, states that DEET is approved for use on children with no age restriction or percentage of DEET in the product; however, DEET should not be applied by children under 10 and application should follow the guidelines stated on specific product labels. The CDC concurs with this use profile, yet qualifies that DEET may be used on children and infants older than 2 months. The American Academy of Pediatrics recommends that products used on children should contain no more than 30% DEET and that DEET should not be used on infants under 2 months of age."*

COMMENT: In Section 6.6 regarding exposure of DEET to children, the Reviewer suggests adding the following: "The American Academy of 12 Pediatrics recommends that repellents should contain no more

than 30% DEET when used on children. Insect repellents also are not recommended for children younger than 2 months."

RESPONSE: *No change was made. This was addressed in the previous section; please see previous response.*

COMMENT: In Section 6.8.1 regarding data needs of exposure studies of DEET in children, the Reviewer suggests removing the phrase "expected to be" from the statement.

RESPONSE: *The change was made as suggested.*

Comments provided by Peer Reviewer #2:

General Comment and Response

COMMENT: The Reviewer provided a review article on DEET by Schoenig and Osimitz (2001) and suggested citing it throughout the toxicological profile as well as incorporating into the profile information from unpublished studies on DEET summarized in the review.

RESPONSE: *In accordance with guidance, ATSDR has added the Schoenig and Osimitz (2001) citation where other review articles are cited, but not as a citation for individual studies, either published or unpublished. Five unpublished toxicokinetics studies (one in humans and four in animals) that the Reviewer specifically suggested adding to the profile have been requested from the conducting laboratory and/or the study sponsor. If ATSDR is able to obtain these studies, pertinent information will be added to the post-public comment version of the profile after the studies are peer-reviewed.*

Minor editorial revisions to the text suggested by the Reviewer (i.e., add a missing word, correct typographical errors, etc.) were done as suggested and are not listed individually below.

CHAPTER 1

COMMENT: The Reviewer commented "Considering EPA has found DEET in 2 of the 1,699 current or former NPL sites, an ATSDR Toxicological Profile for DEET should be a very low priority. The rationale provided in this paragraph does not support preparation of an ATSDR Toxicological Profile as a priority."

RESPONSE: ***"****The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(l) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list." In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(l)(B), to respond for requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.*

COMMENT: Regarding the sentence "This information is important; these future sites may be sources of exposure, and exposure to DEET may be harmful," the Reviewer commented: "This perspective is not justified as a Public Health Statement for DEET because 1) the paucity of consumer adverse effect reports, considering the billions of product applications that have occurred in the 60 year history of DEET usage, undeniably support the fact that DEET is safe for consumer use, 2) the potential exposures to DEET from NPL sites certainly would be orders of magnitude lower than consumers routinely see from use of insect repellents, and 3) the portion of the population possibly exposed to DEET from a few NPL sites would surely be insignificant compared to the approximately 30% of the population that uses DEET insect repellents routinely."

RESPONSE: *Chapter 1 has been revised and the statement "This information is important; these future sites may be sources of exposure, and exposure to DEET may be harmful" is no longer present.*

COMMENT: The Reviewer notes that "Repellant and repellent used interchangeably in the document. Although both are acceptable, it is more appropriate to use consistent spelling throughout."

RESPONSE: *The document has been updated accordingly.*

COMMENT: The Reviewer suggests adding "lotions and wipes."

RESPONSE: *The change was made as suggested.*

COMMENT: The Reviewer states "Release to air is likely to be negligible since spray products release large droplets (>50 μm) that rapidly settle to the ground and vapor pressure is relatively low."

RESPONSE: *The paragraph has been reworded: "The most important route of exposure to the general population is through dermal contact from intentional application to human skin and clothing of consumer products containing DEET. DEET can be released into the air, water, and soil at places where it is produced or used. DEET is most often released into surface waters following its incomplete removal at waste water treatment facilities, and to a lesser extent or released into the air when applying DEET-containing repellents. You could potentially be exposed to DEET if you use a groundwater well that is close to a landfill or surface water for drinking or bathing; the levels of DEET detected in water and air, however, are typically low."*

COMMENT: The Reviewer indicates that "Aronson says 'The rate of evaporation from the skin of humans was reported to be 9.6% in 1 h (Spencer et al. 1979). The amount evaporated was conservatively assumed to be 25% for the purpose of modeling.' Suggest adding Spencer reference here and in Section 2.1."

RESPONSE: *The sentence was reworded and the reference was added: "In its use as an insect or acarid repellent, it has been reported that evaporation from human skin is 9.6% in 1 hour and it is estimated that about 25% of the applied product evaporates into the air (Aronson et al. 2012; Spencer et al. 1979)." In addition, a sentence was added to Section 6.2.1: "It has been reported that evaporation from human skin is 9.6% in 1 hour and it is estimated that about 25% of the applied product evaporates into the air.*

COMMENT: The Reviewer suggests replacing days with hours (see Selim et al. 1995 and Schoenig and Osimitz 2001).

RESPONSE: *The change was made as suggested.*

COMMENT: "Reported concentrations in water are so low compared to consumer use of insect repellents and water solubility relatively high, so it is more likely that DEET would stay in solution rather than penetrate the skin." The comment refers to the following sentence in the section How DEET enters

your body – Water in Chapter 1: "In addition, if your skin contacts water with DEET in it, you may absorb some DEET through your skin."

RESPONSE: *The sentence in question states that SOME DEET MAY be absorbed: it does not state that DEET WILL be absorbed. No change was made.*

COMMENT: "This statement is inconsistent with (Agricultural) soil on page 2, line 6, which states "…[DEET] detections in soils are infrequent." The comment refers to the following sentence in the section How DEET enters your body – Soil in Chapter 1: "If you accidentally eat soil contaminated with DEET, some of the DEET will enter your body through the digestive tract. In addition, if you touch soil contaminated with DEET, some of the DEET will enter your body through the skin."

RESPONSE: *The sentence in question was revised as follows: "Although rarely found in soil, if you accidentally eat soil contaminated with DEET, some of the DEET will enter your body through the digestive tract. In addition, if you touch soil contaminated with DEET, some of the DEET may enter your body through the skin."*

COMMENT: "This statement is inappropriate here because 1) it is not relevant to the general population since this study was for a unique subpopulation using high doses (i.e. >99th percentile of consumer application rate) of insect repellents and 2) the symptoms were associated with the high doses and not long-term exposure scenario." The comment refers to the following statement: "Workers at a national park who used insect repellents or lotions containing DEET repeatedly during the summer season complained more often of chest pain or wheezing, muscle cramping, skin rashes and blisters, dizziness, disorientation, and difficulty concentrating than workers who used the products less often or did not use them at all (NIOSH 1986)."

RESPONSE: *It is within ATSDR's guidance to mention results from studies in workers in Chapter 1. As a result of comments made by another reviewer, the text was revised as follows: "Workers at a national park who used insect repellents or lotions containing DEET repeatedly during the summer season complained more often of chest pain or wheezing, muscle cramping, skin rashes and blisters, dizziness, disorientation, and difficulty concentrating than workers who used the products less often or did not use them at all (NIOSH 1986). Because exposure was inferred from only survey responses, a notable weakness, the findings from this report should be interpreted with caution."*

COMMENT: "This statement is inappropriate for the section title 'Exposure effects for children generally' because it has been determined that these cases were most likely due to overexposure from product misuse/abuse rather than the normal and intended use of DEET insect repellents. Also, if the primary purpose of this Toxicological Profile is to address potential exposure from NPL sites, exposure levels at those sites would be orders of magnitude lower than the extremely high doses necessary to result in serious adverse effects." The comment refers a sentence indicating that neurological effects have been observed in some children following exposure to products containing DEET.

RESPONSE: *As a result of comment from another reviewer, the following text was added: "In the specific case of seizures, it should be noted that because a relatively high percentage (23–29%) of children are exposed to DEET in North America and because seizure disorders occur in 3–5% of children, it would not be unexpected to see an association just by chance (EPA 1998b; Koren et al. 2003)." The added text is very similar to text suggested by another reviewer.*

CHAPTER 2

COMMENT: The Reviewer suggests adding a sentence to the summary of neurological effects stating that the histopathological finding of Abdel-Rahman et al. (2001) have been criticized because of possible methodological flaws.

RESPONSE: *Text provided by the Reviewer was added to the discussion.*

COMMENT: "There are no data to support this speculative statement. Since the body weights were lower towards the end of the lactation period when pups began to transition from milk to diet, it is more likely that the unpleasant taste of DEET reduced their intake due to unpalatability." The comment refers to the following sentence: "Since birth weight was not significantly affected, the reduced body weight of the pups could have been due to reduced milk production or quality, or transfer of DEET and/or metabolites in the milk to the pups."

RESPONSE: *The sentence in question was deleted.*

COMMENT: "Additional data are cited in EPA 1998b; Schoenig and Osimitz 2001." The comment refers to the following sentence: "The animal data are restricted to only a few studies with significant limitations," which appears at the beginning of the discussion of possible inhalation MRLs.

RESPONSE: *Neither EPA (1998b) nor Schoenig and Osimitz (2001) discuss inhalation studies in animals.*

COMMENT: "See Macko and Bergman 1980; Schoenig and Osimitz 2001." The comment refers to a paragraph that states that only one inhalation study was available for review.

RESPONSE: *The inhalation study in rats and dogs by Macko and Bergman was added to the profile; it is cited as Army (1980a). As mentioned above, Schoenig and Osimitz (2001) do not mention inhalation studies.*

CHAPTER 3

COMMENT: "See Keil et al. 2009 on a screening evaluation for humoral immunological function in B6C3F1 mice." The comment refers to a sentence at the end of the summary of immunological effects by oral exposure stating that none of the animal studies mentioned conducted tests to examine immune competence.

RESPONSE: *Keil et al. (2009) administered DEET to mice by subcutaneous injection, a non-relevant route of exposure. The lack of studies by dermal exposure, the most relevant route for humans, is acknowledged in the Section 3.12.2, Identification of Data Needs.*

COMMENT: "These symptoms suggest inhalation exposures rather than solely dermal exposures. Were other factors controlled in the study: smoking, allergies, recreational drugs?" The comment refers to the following sentence regarding the NIOSH (1986) study of park employees in Florida: "The survey

found that complaints of chest pain or wheezing were significantly elevated ($p<0.05$) in the high-exposure group (30%) compared to the medium- (9%) or low-exposure (11%) groups."

RESPONSE: *The study controlled for smoking, but not for allergies or recreational drug use. Text was added indicating that because exposure was inferred from only survey responses, a notable weakness, the findings from this report should be interpreted with caution. This is also mentioned in Chapters 1 and 2.*

COMMENT: The Reviewer provided revised text for the section on renal effects in rats by dermal exposure. The text states that the nephropathy observed in male rats is specific to male rats and not relevant to human health effects.

RESPONSE: *The paragraph underwent extensive revisions with the addition of results from the EPA (1988) dermal study in rats. A statement was also added regarding the lack of relevance of the male rat nephropathy to human risk assessment.*

COMMENT: The Reviewer suggests adding the following to the first paragraph of dermal effects by dermal exposure: "The paucity of consumer adverse effect reports, considering the billions of product applications that have occurred in the 60 year history of DEET usage as an insect repellent active ingredient, undeniably support the fact that DEET is safe for consumer use."

RESPONSE: *A slightly modified statement was added: "It should be noted, however, that the paucity of consumer adverse effect reports, considering the billions of product applications that have occurred in the 60 year history of DEET usage as an active ingredient in insect and acarid repellent, suggests that DEET is safe for consumer use."*

COMMENT: The Reviewer suggests moving a discussion of ocular effects in animals following application of liquid DEET directly to the eye to another part of the document because application was not to the skin.

RESPONSE: *There is no other part of the document to discuss effects that were not due to inhalation or ingestion of the substance. Traditionally, ocular effects due to direct contact of a substance with the eye are discussed under dermal exposure.*

COMMENT: "Also, see Keil et al. 2009 on a screening evaluation for humoral immunological function in B6C3F1 mice." The comment refers to Section 3.2.3.3, Immunological and Lymphoreticular Effects.

RESPONSE: *Keil et al. (2009) administered DEET to mice by subcutaneous injection, a non-relevant route of exposure. The lack of studies by dermal exposure, the most relevant route for humans, is acknowledged in Section 3.12.2, Identification of Data Needs.*

COMMENT: "Considering the hundreds of millions of consumers and billions of applications of DEET products, the incidence of these reports is exceedingly low." The comment refers to the first sentence of Section 3.2.3.4, Neurological Effects, stating that there are many reports of adverse neurological effects in humans following application of insect repellents containing DEET.

RESPONSE: As a result of another reviewer's comment, the sentence was changed *to "There have been sporadic reports over the last several decades of adverse…"*

COMMENT: Regarding the studies of Abou-Donia and coworkers, the Reviewer suggests adding a statement in the Neurological Effects section indicating that the studies have been criticized because of some flaws in the methodology used to prepare brain samples for microscopic examination.

RESPONSE: *The text suggested by the Reviewer was added with slight modifications.*

COMMENT: "Speculative and not supported by the totality-of-the-evidence." The comment refers to the following sentence in Section 3.2.3.6, Developmental Effects: "Although a causal relationship with DEET was not established, DEET might have played a role based on the fact that studies in animals have described transfer to the fetus."

RESPONSE: *The sentence was revised as suggested by the Reviewer.*

COMMENT: Regarding Section 3.3, Genotoxicity, the Reviewer suggests looking at the review by Schoenig and Osimitz (2001), presumably for additional information.

RESPONSE: *Three unpublished studies briefly summarized in Schoenig and Osimitz (2001) are cited in the toxicological profile as EPA (1990c). ATSDR obtained the studies form EPA; however, because of contractual agreements, only information from Data Evaluation Records (DER) could be cited in the profile.*

COMMENT: "This contradicts other authors who concluded that, if anything, formulation with ethanol enhances dermal penetration and dermal absorption of DEET." The comment refers to the following sentence regarding a toxicokinetics study by Fediuk et al. (2011): "The study authors attributed the low bioavailability in this study to the use of the ethanol vehicle, which enhances evaporation."

RESPONSE: *The sentence expresses the opinion of Fediuk et al. (2011) based on results from a study that they cite.*

COMMENT: The Reviewer suggests adding text regarding the dermal absorption of DEET in combination with sunscreen from studies by Wang and Gu (2007), Gu et al. (2005), and Santhanam et al. 2005), which are cited in the profile.

RESPONSE: *The suggested text was added.*

COMMENT: Regarding Table 3-4, Species Differences in *In Vitro* Estimates of DEET Dermal Permeability, the Reviewer has the following comment: "Available *in vivo* data should be summarized in a similar table as more realistic and relevant to human exposure potential."

RESPONSE: *ATSDR will consider adding a table with human data to the post-public version of the profile.*

COMMENT: The Reviewer suggests adding text regarding distribution of radioactivity to tissues to Section 3.4.2.2, Oral Exposure.

RESPONSE: *The suggested text was added.*

COMMENT: "Not clear how two test concentrations give one value for each CYP isoform." The comment refers to Table 3-5, which shows activity of various CYP isoforms incubated with DEET.

RESPONSE: *It appears that the CYPs were incubated with DEET at either 1,000 or 3,000 µM, but not both. Usmani et al. (2002) do not specify which CYP was incubated with what DEET concentration.*

COMMENT: The Reviewer notes: "10.4 g is a huge dose of DEET since the 50th percentile rate for consumer application is about 1 g. It is likely unchanged DEET was detected in the urine because metabolism pathways had been saturated. Suggest this context be added to the text." The comment refers to the following paragraph: "Wu et al. (1979) measured DEET in the urine of a 30-year-old, 78-kg subject who applied 10.4 g of DEET in a repellent to ~75% of his body. The duration of treatment was not specified. The rate of excretion of unchanged DEET via urine was reported to be 10–14% in the first hour and 2% in the fourth hour. Unchanged DEET was detected in the urine up to 18 hours after application."

RESPONSE: *The following text was added: "Because 10.4 g is a very high dose, which may have caused saturation of metabolism pathways, Wu et al. (1979) probably detected unchanged DEET in the urine."*

COMMENT: "2-3 days of incubation is irrelevant since DEET is metabolized within a few hours *in vivo*. If this study is not deleted, it needs to be put into perspective with what is known about metabolism and elimination of absorbed DEET." The comment refers to the following sentence in Section 3.5.1, Pharmacokinetic Mechanisms: "In contrast, Kasting et al. (2008) used an equilibrium dialysis method to estimate that ~81% of DEET is bound to BSA; equilibrium was reached at about 2–3 days of incubation, suggesting that the incubation time may have been too short in the earlier study."

RESPONSE: *The following sentence was added: "The significance of equilibrium being reached in days is unclear since dermally applied DEET in humans is eliminated within hours (Selim et al. 1995)."*

COMMENT: The Reviewer suggests adding text at the beginning of Section 3.5.2, Mechanisms of Toxicity, indicating that in some cases, the seizures in children may be coincidental with exposure to DEET rather than caused by DEET exposure given that idiopathic seizures in children are not uncommon.

RESPONSE: *The text suggested by the Reviewer appears in several places in the profile. Section 3.5.2 is not the appropriate place to include it.*

COMMENT: "Do not believe this is accurate." The comment refers to the following sentence: "Although the mechanism(s) involved have not been elucidated, plausible explanations have been proposed."

RESPONSE: *The sentence in question was deleted.*

COMMENT: The Reviewer notes: "These are speculative hypotheses by the authors in the context of their publication, but they do not belong in the Toxicological Profile until substantiated by these or other investigators."

RESPONSE: *ATSDR agrees that these are speculative hypotheses, but as long as this is made clear, it is appropriate to include them in this section of the profile. The text was revised so that the sentence begins as follows: "Although these are speculative hypotheses, the investigators proposed…"*

COMMENT: The Reviewer proposed text to be added at the end of the discussion of the Abou-Donia and coworkers studies stating that these studies have been criticized on the grounds of methodological flaws.

RESPONSE: *The proposed text was added*.

COMMENT: In the Children's Susceptibility section, the Reviewer suggests quoting text from the EPA's RED for DEET regarding the possibility that some cases of seizures in children following exposure to DEET may have been coincidental.

RESPONSE: *The suggested text was added*.

COMMENT: "There are no data to support this speculative statement." The statement in question is the following: "Since birth weight was not significantly affected, the reduced body weight in the pups could have been due to reduced milk production or quality, or transfer of DEET and/or metabolites in the milk to the pups." The Reviewer suggests adding the following: "However, it is more likely that the unpleasant taste of DEET reduced the intake of diet by the pups due to unpalatability, since the body weights were lower towards the end of the lactation period when pups begin to transition primary nutrition from milk to diet available to mothers."

RESPONSE: *The suggested text is as speculative as what is in the profile. The sentence that was in the profile was deleted.*

COMMENT: The Reviewer suggests adding text in Section 3.9, Interactions with Other Chemicals, stating that the results of studies of interactions between DEET and other chemicals conducted by Abou-Donia and coworkers may have been misinterpreted due to methodological flaws. The Reviewer suggests adding the same text in two places.

RESPONSE: *Adding the suggested text in one place seemed sufficient.*

COMMENT: "Speculative statement not appropriate for the Toxicological Profile." The comment refers to the following sentence: "It was suggested that in combined treatments, competition for liver and plasma detoxifying enzymes by the test chemicals decreases their breakdown rate and increases their delivery to the brain." This was suggested by Abdel-Rahman et al. (2004) as a possible explanation for their results.

RESPONSE: *The sentence was deleted.*

COMMENT: The Reviewer notes that a human study by Roy et al. (2006) is discussed in Section 3.9, Interactions with Other Chemicals, after the discussion of animal studies and suggests moving it to the beginning of the section, as discussion of human studies normally precedes animal studies in toxicological profiles.

RESPONSE: *The Reviewer is correct in that human studies typically precede animal studies. However, it was felt that since Roy et al. (2006) is a more recent study than those of Abou-Donia and coworkers and refutes the earlier findings of Abou-Donia and coworkers regarding interactions between DEET, permethrin, and pyridostigmine bromide, it would be best placed after the animal studies.*

COMMENT: "Speculative statement." The comment refers to the following sentence: "The investigators suggested that possible mechanisms could involve facilitated absorption of PB in the gut by DEET or inhibition of detoxification systems." The sentence in question refers to a study by McCain et al. (1997) that also examined interactions between DEET, permethrin, and pyridostigmine bromide. The Reviewer suggests deleting the sentence.

RESPONSE: *The sentence just states what the investigators suggested. It is only a suggestion, not a definite statement. No change was made.*

COMMENT: "Speculative statement." The comment refers to the following paragraph: "The investigators noted that the primary cause of death appeared to be circulatory failure and proposed the following sequence of events: DEET may have depressed central cardiorespiratory centers and altered sympathetic outflow from the brain. PB aggravated DEET-induced toxicity presumably by promoting accumulation of acetylcholine at peripheral cholinergic receptor sites. This accumulation at cholinergic sites resulted in bradycardia and further reduced cardiac output, which caused the development of progressive circulatory shock." This paragraph refers to results by Chaney et al. (2002) who studied interactions between DEET and pyridostigmine bromide in rats. The Reviewer suggests deleting the paragraph.

RESPONSE: *The paragraph is speculative, but again, it is only a proposed sequence of events. The investigators are not stating that their results can only be explained by the proposed sequence of events. No change was made.*

COMMENT: "Inhalation and oral are very minor potential routes of exposure compared to dermal." The comment refers to the following sentence that appears in Section 3.12.1, Existing Information on Health Effects of DEET: "The intake and uptake rates from oral exposure, however, is faster than those by the dermal route of exposure, so greater peak concentrations in liver and nervous system tissues can be achieved." The Reviewer suggests deleting: "… so greater peak concentrations in liver and nervous system tissues can be achieved."

RESPONSE: *ATSDR agrees with the Reviewer in that the oral and inhalation routes of exposure are much less important than the dermal route when DEET repellents are used as intended. However, ATSDR sees no compelling reason to delete the text in question. In fact, in Section 3.4.2.2, the Reviewer suggests adding the following text: "The percent of administered radioactivity reaching systemic*

circulation and the tissues was much higher for animals administered [^{14}C]DEET orally than for animals administered [^{14}C]DEET dermally (Schoenig et al. 1996)."

COMMENT: The Reviewer suggests adding the following statement: "The toxicological database is considered adequate for characterizing hazard and assessing risk from DEET. No additional studies are anticipated to be needed for registration review." This is a quotation from EPA's (2014), "DEET (N,N-diethyl-meta-toluamide) Combined Work Plan, Summary Document, and Proposed Interim Registration Review Decision."

RESPONSE: *EPA's statement is specific for studies that fill needs for the registration review process. ATSDR's scope is wider. As stated in Section 3.12, data gaps are "…defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed." No change was made.*

COMMENT: In the Data Needs section under Intermediate-Duration Exposures, the Reviewer suggests making reference to a Keil et al. (2009) study in support for the existence of immunological data for this particular duration of exposure.

RESPONSE: *Keil et al. (2009) is a study that investigated immunological effects in mice that received subcutaneous injections of DEET for 14 days. Because of the non-relevant route of exposure used in the study, the findings are not discussed in the profile; it is now mentioned in the Immunotoxicity section of Data Needs.*

COMMENT: In the Data Needs section under Intermediate-Duration Exposures, the Reviewer suggests making reference to Schoenig et al. (1994) study in support for the existence of developmental data for this particular duration of exposure.

RESPONSE: *Schoenig et al. (1994) is a publication of two developmental studies, one in rats and one in rabbits. Both are acute-duration studies; therefore, Schoenig et al. (1994) is mentioned in Acute-Duration Exposure of the Data Needs section. No changes were made.*

COMMENT: "See Schoenig et al. 1993; Schoenig and Osimitz 2001." The comment refers to the following sentence in the Chronic-Duration Exposure and Cancer of the Data Needs: "In addition, the available studies did not test for end points such as subtle neurobehavioral effects, which have been reported at relative low doses in intermediate-duration dermal studies in rats (Abou-Donia et al. 2001a)."

RESPONSE: *Schoenig et al. (1993) conducted neurobehavioral tests in rats exposed to DEET once and in F2 rats from a 2-generation study that were exposed for an intermediate-duration period. No subtle neurobehavioral end points were examined in the chronic-duration studies in rats and mice. No changes were made.*

COMMENT: The comment refers to the following sentence: "Since the birth weight of pups was not significantly different from controls, the possibility exists that DEET was transferred to the pups via the milk or that there was insufficient milk production by the exposed dams, or both." The Reviewer

suggests adding the following: "However, it is more likely that the unpleasant taste of DEET reduced the intake of diet by the pups due to unpalatability, since the body weights were lower towards the end of the lactation period when pups begin to transition primary nutrition from milk to diet available to mothers."

RESPONSE: *The suggested addition is just as (or more) speculative than the current text and was not added; however, the sentence in question was deleted.*

COMMENT: "See Keil et al. 2009 on a screening evaluation for humoral immunological function in B6C3F1 mice." The comment appears in the Immunotoxicity section of the Data Needs section.

RESPONSE: *Text was added indicating that Keil et al. (2009) reported altered immunocompetence in mice following subcutaneous injection DEET and that studies by the a relevant route of exposure, the dermal route, would be useful.*

COMMENT: "See Osimitz et al. 2010; Pegus study in Schoenig and Osimitz 2001." The comment refers to the following sentence in the Neurotoxicity section of Data Needs: "Follow-up of the individuals with the most severe effects (i.e., seizures) would provide valuable information regarding possible long-term effects (or lack thereof) due to acute exposure."

RESPONSE: *Text was added indicating that results from a 1-year follow-up of 35 seizure cases were reported in Osimitz et al. (2010) and continued follow-up of these and new cases would be useful.*

COMMENT: The Reviewer provided text to add in the Neurotoxicity section regarding the criticism of the histological findings from Abdel-Rahman et al. (2001, 2004) by Jortner (2006). The Reviewer has suggested including this same text in several places in the profile.

RESPONSE: *The following text was added: "With regard specifically to morphological alterations, as mentioned earlier, findings reported by Abdel-Rahman et al (2001, 2004) have been questioned as possible artifacts (Jortner 2006), so it would be useful to try to replicate their findings."*

COMMENT: "Totality-of-the-evidence seems to indicate that the neurological alterations are transient narcosis correlated with Cmax blood levels of DEET following oral exposure." The comment refers to the following sentence: "The mechanism by which DEET (or a metabolite) induces neurological alterations has not been elucidated, so further research in this area is needed."

RESPONSE: *ATSDR disagrees that the neurological alterations represent transient narcosis since the principal manifestations in humans following high-exposure are tremors and seizures. No change was made.*

COMMENT: The comment refers to the following sentence: "… since birth weight was not affected by treatment with DEET, the reduced body weight in the pups could have been due to reduced milk production or quality, or transfer of DEET and/or metabolites in the milk to the pups." The Reviewer suggests adding the following: "However, it is more likely that the unpleasant taste of DEET reduced the intake of diet by the pups due to unpalatability, since the body weights were lower towards the end of the lactation period when pups begin to transition primary nutrition from milk to diet available to mothers."

RESPONSE: *The text provided by the Reviewer is as speculative as the sentence in question, which was deleted.*

CHAPTER 6

COMMENT: In Section 6.5, the Reviewer notes that some data are from the same study as above starting with "In 1991,…"

RESPONSE: *The original source could not be retrieved; therefore, both papers were cited with reported highlights.*

COMMENT: In Section 6.5, the Reviewer suggests replacing "days" with "applications."

RESPONSE: *No change was made. The reference does not specify that the product was applied that many times, only that it was used that many days; the number of applications during the day is not reported here.*

COMMENT: In Section 6.6, the Reviewer suggests deleting some of the text that is not relevant to this section.

RESPONSE: *Instead of deleting the text, the phrase "in comparison to estimates of" was added.*

COMMENT: In Section 6.6, the Reviewer suggests replacing "specific" with "individual."

RESPONSE: *The change was made as suggested.*

COMMENT: In Section 6.6, the Reviewer suggests adding "although these are judged to be minor."

RESPONSE: *The change was made as suggested.*

COMMENT: In Section 7.1, the Reviewer suggests adding dermal, following dermal application.

RESPONSE: *No change was made. Application is not always strictly dermal; products may be applied to clothing, and products that are impregnated may be worn.*

COMMENT: In Section 7.1, the Reviewer suggests deleting Sudakin and Trevathan (2003) and adding Blomquist and Thorsell (1977) and Feldman and Maibach (1970).

RESPONSE: *The change was made as suggested.*

COMMENT: In Section 7.1, the Reviewer suggests replacing the word "probability" with "possibility."

RESPONSE: *The change was made as suggested.*

COMMENT: The Reviewer notes that there is no footnote “a” at the bottom of the Table 7-1.

RESPONSE: *The footnote in question was removed.*

COMMENT: The Reviewer notes that there is no footnote “a” at the bottom of the Table 7-2.

RESPONSE: *The footnote in question was removed.*

Comments provided by Peer Reviewer #3:

GENERAL COMMENTS

COMMENT 1: The Reviewer notes: "The document reads as if it has been written by more than one author. Before preparing the final report, one author should re-read entire document and put it into one style. The difference in styles is most clear in Chapter 3, Health Effects. The first half has much longer sentences, more grammatical errors (sentences starting with "however"), and describes experimental animals differently (dogs vs beagles or beagle dogs) from the latter half of the chapter. In general the paragraphs are too long and need to be broken down (e.g., don't put all routes of administration into one paragraph). Sentences are too long (for example, see page 40, lines 9-18). To catch and correct a number of simple spelling mistakes, etc. Spellcheck should be run. The style in the second of Chapter 3 is preferable."

RESPONSE: *The document was written by more than one person, as it is always the case in toxicological profiles. A single author wrote Chapter 3, except for Section 3.4, Toxicokinetics. ATSDR has revised the sentences starting with the word "however" throughout the document. Without specific examples, it is unclear what the Reviewer means by "putting all routes of administration into one paragraph." ATSDR disagrees with the Reviewer's assertion that sentences on page 40, lines 9–18 are too long. There are five sentences in the 10-line paragraph, an average of only two lines per sentence. Spellcheck was run in the revised draft to detect spelling errors.*

COMMENT 2: The Reviewer notes: "For studies included in Tables 3-1 (sample only) and 3-2 (which is not included) the studies included are described as "reliable". No definition of what a "reliable" study is provided. A definition of this term should be provided. (See for example, page 26, lines 12 & 19). The use of this terminology without a definition makes the document sound judgmental."

RESPONSE: *Reliable studies are those that test a sufficient number of animals, use controls, use appropriate statistical methods, and have a design appropriate to answer the main questions posed. A definition of what constitutes a reliable study does not seem necessary in the profile.*

COMMENT 3: The Reviewer notes: "In Chapter 3, the first route of administration covered is inhalation. The route for which there is the least data and for which there are no deaths. The routes (e.g., oral, dermal, i.v.) that have more significant health effects, including death, seem to be buried in the middle of Chapter 3. Unless the organizational structure cannot be changed, I would start with oral data and end with inhalation."

RESPONSE: *ATSDR understands the Reviewer's concern, but the structure of the toxicological profiles is set so the discussion of effects follows the sequence inhalation/oral/dermal. This is standard in all profiles.*

COMMENT 4: The Reviewer notes: "It is not clear why a number of standard scientific terminology are not used in the text (i.v., i.p., V_d, $t_{1/2}$) but on occasion an abbreviation is introduced and never used again. Also, there is at least two abbreviations in the text that are not in the Appendix, i.e., PB for Pyridostigmine Bromide and V_d for volume of distribution, are missing."

RESPONSE: *According to ATSDR's guidance, common terms such as intravenous, intraperitoneal, and others should not be abbreviated. Terms such as volume of distribution or half-life can be abbreviated if*

they appear repeatedly throughout the document. The profile was revised to comply with these general guidelines. The acronyms, abbreviations, and symbols listed in Appendix C represent a standard set that appears in each toxicological profile.

COMMENT 5: The Reviewer notes: "At times the authors seem to have used judgmental words when interpreting the data or comparing data from multiple studies or making statements in the absences of data (For example, see page 23, line 23; page 26, lines 1-2; page 31, line 11). On page 23, line 23, the author of this report states that "the findings from this study are questionable". The findings are not questionable. The findings are the findings. What is questionable are the doses that are difficult to know and dose is associated with the findings."

RESPONSE: *ATSDR agrees with the Reviewer in that the word "questionable" on page 23, line 23 may have been inappropriate and was changed with the word "unreliable." The word "questionable" also appears on page 26, lines 1-2, as the Reviewer notes. In this case, it was the word used in the paper by the study author, and this is now noted in the profile. On page 31, line 11 the text states that an 18-month-old child ingested an unknown, but probably small, amount of an insect repellent containing DEET. The phrase "but probably small" was used by the study author, Zadikoff (1979), and this is now noted in the revised text.*

COMMENT 6: The Reviewer notes: "Repellent is spelled in two different ways in the document. Author(s) should decide whether it is: repellent or repellant."

RESPONSE: *The revised profile uses only the word "repellent."*

COMMENT 7: The Reviewer notes: "The handling of abbreviations in the document is inconsistent. Some abbreviations are not defined in the text and are not in Appendix C. Other abbreviations are used in the Tables/Figures and are not defined in the text, Tables/Figures footnotes or Appendix C. In other cases, abbreviations are used in Tables/Figures and defined in a footnote but not included in Appendix C. Ideally, all abbreviations would be defined at time of first use and included in Appendix C."

RESPONSE: As mentioned in the response to Comment 4 above, the acronyms, abbreviations, and symbols listed in Appendix C represent a standard set that appears in each toxicological profile and are not typically modified. Other abbreviations that appear in the text, tables, or figures are defined at the time of first use.

COMMENT 8: The Reviewer notes: "The text of the document has been reviewed for inclusion of abbreviations in Appendix C Acronyms, Abbreviations, and Symbols. A number of omissions were identified and noted in the Reviewer's summary below."

RESPONSE: *ATSDR would like to thank the Reviewer for pointing out inconsistencies regarding abbreviations in the toxicological profile. As indicated earlier, however, Appendix C is not typically modified.*

COMMENT 9: The Reviewer notes: "The references section of the report has been matched against the text of the report. There appear to be some errors in the references as cited in the text. These errors are

noted below. There references in the Section 8. References (marked with an *) that are **not** cited in the body of the report."

RESPONSE: *ATSDR would like to thank the Reviewer for pointing out errors in the references section. The errors have been corrected.*

SPECIFIC COMMENTS

COMMENT: Pxi, L12: The comment refers to the sentence "These experts collectively have knowledge of DEET's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans." This sentence appears on the page that lists the peer Reviewers for the profile. The Reviewer suggests revising the sentence as follows: "These experts collectively have knowledge of physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans of DEET."

RESPONSE: *The sentence in question is boilerplate text.*

COMMENT: Pxi, L18: The comment refers to the sentence "Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed…" The Reviewer notes that earlier text already provided the abbreviation for Agency for Toxic Substances and Disease Registry so the agency's full name is not necessary here.

RESPONSE: *This is part of the standard format of the toxicological profiles. The Reviewer's suggestion, however, will be considered for future profiles.*

COMMENT: Pxvii and xix: The Reviewer asks why the list of figures appears before the list of tables. The Reviewer states that the reverse is usually expected.

RESPONSE: *This is the established format for toxicological profiles.*

COMMENT: Table 3-1: The Reviewer states that only an example of Table 3-1 is provided and no Table 3-2 is presented.

RESPONSE: *The Reviewer may be referring to the example table that appears in Appendix B, User's Guide. That table is labeled Table 3-1; it is just an example of an LSE table. There is no need for a Table 3-2.*

ATSDR noted that the Reviewer had a great number of editorial comments on the text of the toxicological profile. For example, the Reviewer noted words misspelled, words missing, spaces missing between words, sentences misconstructed, etc. ATSDR would like to thank the Reviewer for carefully reading the document and providing corrected or alternative text. Because of the high number of these types of comments, they are not listed individually below; however, all the revisions suggested by the Reviewer were done.

COMMENTS ON CHAPTER 1

COMMENT: P1, Introduction, paragraph 2, sentence 1: Regarding the text "…DEET (N,N-diethyl-*meta*-toluamide), an insect and acarid repellant," the Reviewer comments: "Why does the author at times refer to DEET as an insect and acarid repellent and at others as an insect repellent or insecticide? If the author is at all times referring to both uses, the author could insert could insert a parenthetical phrase stating '…DEET, an insect and acarid repellent (referred to in the remaining text as an insect repellent or insecticide).'"

RESPONSE: *The part of the comment: DEET …insect and acarid... has been corrected where appropriate. A search through the body of report did not find instances where the 'insecticide' part of comment applies; it appears that where insecticide is used in the report, it is appropriate in the context of the sentence.*

COMMENT: P1, Why a DEET release can be harmful, paragraph 2, sentence 1: The Reviewer suggests changing the text to: "…DEET, you may not…"

RESPONSE: *The change was not made; this is standard ATSDR boilerplate text.*

COMMENT: P1,Why a DEET release can be harmful, paragraph 2, sentence 2: The Reviewer suggests changing the text to: "…and how you happen to come in contact with it."

RESPONSE: *The change was not made; this is standard ATSDR boilerplate text.*

COMMENT: P1,Why a DEET release can be harmful, paragraph 2, sentence 3: The Reviewer suggests changing the text to: "…on whether you have been"

RESPONSE: *The change was not made; this is standard ATSDR boilerplate text.*

COMMENT: Page 2,What is DEET, sentence 3: The Reviewer suggests adding parenthetically some examples of these DEET products in the text "…in some common repellants…"

RESPONSE: *OFF and Cutter were added as examples.*

COMMENT: P2, How is DEET used, paragraph 1, sentence 2: The Reviewer suggests adding parenthetically some examples of these DEET products in the text "…DEET formulations…."

RESPONSE: *No change was made; examples are included (sprays, mists etc.).*

COMMENT: P2, How is DEET used, paragraph 2: The Reviewer suggests changing the text to: "DEET has been previously and is currently sold as an ingredient in…."

RESPONSE: *This change was made as suggested.*

COMMENT: P3: The Reviewer asks why the table on this page is not numbered.

RESPONSE: *The format of Chapter 1 was changed from table form to narrative text.*

COMMENT: P3, Table, Row "Air" and Column "Possible Exposure Pathway": The Reviewer suggests the use of "…have not…" instead of "haven't" and noted that: "It is noted that in a numerous places the use of contractions that are not appropriate in formal documents. Some of these have been noted in the review, but may not have found all of their occurrences."

RESPONSE: *The text throughout the entire profile was checked and revised accordingly*.

COMMENT: P4, Introduction to DEET health effects, sentence 2: The Reviewer notes that a word appears to be missing in the phrase"…through contract….," and questions "Contact with what?"

RESPONSE: *The following text was inserted after the word contact: "…with products containing DEET."*

COMMENT: P5, Exposure effects for children generally, sentence 1: The Reviewer suggests adding a few examples of the types neurological effects observed; i.e., "...the same type of neurological effects (e.g., ?, ?, ?) observed in adults…"

RESPONSE: *Specific neurological effects were added.*

COMMENT: P6/Food, sentence 3: Regarding the text "…Do not let young children apply DEET…," the Reviewer suggests defining an age for young children.

RESPONSE: *The change was made as suggested.*

COMMENT: P6/Food, sentence 4: The Reviewer suggests changing the text to: "Do not re-use DEET containers, especially for storing food and water."

RESPONSE: *The change was made as suggested.*

COMMENT: P6, Drinking Water: The Reviewer suggests breaking the one sentence into two sentences by inserting a period after the Benotti reference and rewriting the second half of sentence as "When it is detected, however, it is usually at low concentrations…"

RESPONSE: *The change was made as suggested.*

COMMENT: P6, Contaminated groundwater or solid: The Reviewer suggests making the one sentence less complex and introducing a period after "…for drinking or bathing." "The levels of DEET detected in water, however, were typically low."

RESPONSE: *The change was made as suggested.*

COMMENT: P7, The federal government regulates toxic substances and The Federal government recommends safe toxic substance practices: The Reviewer notes that OSHA, ATSDR, and NIOSH have already been defined earlier in report and the defining text should be deleted in this sections.

RESPONSE: *As indicated earlier, the format of Chapter 1 will change to narrative text, and there will not be duplication of definitions.*

COMMENT: P7: The Reviewer questions why the table is not numbered and suggests numbering it. In addition, the Reviewer indicates that OSHA and NIOSH don't need to be defined here as they have already been defined.

RESPONSE: *The current format of Chapter 1 did not include table numbers. As mentioned in the response to the previous comment, there will not be duplication of definitions in Chapter 1 of the draft for public comment of the profile.*

COMMENT: P7: The Reviewer questions why the % is missing under ACTIVE INGREDIENTS DEET.

RESPONSE: *This is a general statement that is required to be put on labels. The XX.XX would be inserted by the product manufacturer.*

COMMENT: P10, L7: The Reviewer suggests changing the text to: "…DEET was consumed in commercial products…"

RESPONSE: *The change was made as suggested.*

COMMENT: P10, L9: The Reviewer suggests changing the text "5-7" to "5 to 7."

RESPONSE: *The change was made as suggested.*

COMMENT: P10, L11: The Reviewer suggests changing the text to: "This contribution results from washing skin…" and notes that "This" used alone cannot be used to start a sentence as it is too vague.

RESPONSE: *The change was made as suggested.*

COMMENT: P10, L33: The Reviewer notes that NHANES already defined earlier in the report and suggests deleting the defining text.

RESPONSE: *No change was made because this was not yet defined in the body of the document; it was only previously defined in the list of tables.*

COMMENTS ON CHAPTER 2

COMMENT: P10, L17: The Reviewer suggests changing the text to: "…DEET, however, is considered…

RESPONSE: *The change was made as suggested.*

COMMENT: P10, L25: The Reviewer suggests changing the text "4 to 100% change" to "4% to 100% change."

RESPONSE: *No change was made; ATSDR guidelines specify that units of measure are not repeated in ranges of numbers.*

COMMENT: P10, L29-30: The Reviewer suggests changing the text to: "…DEET absorbed through the skin, however, can transfer…"

RESPONSE: *The change was made as suggested.*

COMMENT: P11, L23: The Reviewer suggests inserting a new paragraph after "…(Koren et al. 2003)." and rewriting the sentence: "There is no reliable information regarding doses or exposure concentrations associated with effects. A survey of 143 employees of the Everglades National Park, Florida and who used DEET regularly in their work, showed that more highly exposed workers…."

RESPONSE: *The change was made as suggested.*

COMMENT: P13, L4: The Reviewer notes that the term "reproductive organs" is vague, assumes that this is referring to female, but could equally be testes, and would like this to be clarified.

RESPONSE: *The text was revised to indicate the sex of the species mentioned.*

COMMENT: P14, L1: The Reviewer notes that MRL was already defined earlier and suggests deleting the defining text here.

RESPONSE: *No change was made; this is standard boilerplate text.*

COMMENT: P15, L17-18: The Reviewer notes that the meaning of the following sentence is unclear, particularly with regard to the phrase "…and were not specified…" and suggests rewriting for clarity: "Because the actual exposure concentrations were 50–60% of the target concentrations, and were not specified, the results of this study are questionable."

RESPONSE: *The sentence was rewritten as follows: "Because the actual exposure concentrations were not specified and, according to the investigators, were 50–60% of the target concentrations, the results of this study are unreliable."*

COMMENT: P16: This page is an example of one that is difficult for a Reviewer to sort out what the author means as the sentences are long and the whole page is one paragraph. Referencing is vague between sentences as to species referred. This page needs substantial rewriting.

RESPONSE: *All of the revisions suggested by the Reviewer regarding page 16 were done.*

COMMENTS ON CHAPTER 3

COMMENT: P21, L16, 26, 28, 32: The Reviewer suggests several editorial changes.

RESPONSE: *Page 21 is boilerplate text, so no changes were made. The Reviewer's suggestions, however, will be considered for future profiles.*

COMMENT: P23, L22: The Reviewer notes that the sentence is awkward and states "The findings aren't questionable. They are what they are. The doses associated with the findings are not clear. Needs to be reworded."

RESPONSE: *The sentence was reworded and the word "questionable" was replaced with "unreliable."*

COMMENT: P24, L2: The Reviewer notes that AAPCC is not in Appendix 3.

RESPONSE: *The Reviewer probably refers to Appendix C, Acronyms, Abbreviations, and Symbols. As previously indicated, the acronyms, abbreviations, and symbols listed in Appendix C represent a standard set that appears in each toxicological profile.*

COMMENT: P24, L32; P25, L1, 2, and 3: Referring to the sentence "No studies were located regarding the following effects," the Reviewer notes that it should be repeated under each of the appropriate sections because it is confusing to be placed in the current location.

RESPONSE: *ATSDR's guidance states that when necessary (as is the case here), subheadings should be collapsed. No changes were made.*

COMMENT: P25, L24: The Reviewer suggests adding the gender of the 8-year-old child.

RESPONSE: *Tenenbein (1987) did not specify the child's gender.*

COMMENT: P26, L1: The Reviewer wonders about the use of the word "questionable" and notes that it is unclear whether this word is the choice of the author of this report of the scientists who conducted the study. The Reviewer further states that "Unless Ambrose 1959 used that word, it should be replaced in the text."

RESPONSE: *The word "questionable" was used by Ambrose (1959).*

COMMENT: P26, L12 and 19: The Reviewer questions the use of the word "reliable" and suggests providing a definition for how some studies were considered reliable and others were not.

RESPONSE: *As stated previously, reliable studies are those that test a sufficient number of animals, use controls, use appropriate statistical methods, and have a design appropriate to answer the main questions posed. A definition of what constitutes a reliable study does not seem necessary in the profile.*

COMMENT: P27, L34-P28, L1-2: The Reviewer suggests deleting the following sentence and notes that the statement re: hematology seems to represent the author's favorable opinion/judgment of DEET safety and not data: "It is likely that hematology tests were conducted in other cases of acute intoxication with DEET, but the results were not reported because they may have been within normal limits."

RESPONSE: *This text was revised: "No explicit statements regarding hematology tests were provided in other cases of acute intoxication with DEET that were reviewed."*

COMMENT: P28, L21-23: The Reviewer suggests deleting the following sentence and notes that the statement re: liver function seems to represent the author's favorable opinion/judgment of DEET safety and not data, as above with hematology: "It is reasonable to assume that liver function tests were probably conducted in other cases and the results were not mentioned in the reports because they may have been within normal limits."

RESPONSE: *This text was revised: "No explicit statements regarding liver function tests were provided in other cases of acute intoxication with DEET that were reviewed."*

COMMENT: P29, L26: The Reviewer requests that the authors' conclusions relative to the nephritis in both treated and control groups of mice be added where the text states "…which occurred in control groups".

RESPONSE: *The authors' (Schoenig et al. 1999) conclusion that the nephritis appeared to be incidental and unrelated to the test material was added to the text.*

COMMENT: P31, L11: The Reviewer suggests changing the text "…but probably small…" and questions whether Zadikoff (1979) states that the dose was probably small or whether that is the conclusion of this report's authors (if the latter, the Reviewer suggests deleting it since it is judgmental).

RESPONSE: *The statement regarding the dose being probably small appears in Zadikoff's report.*

COMMENT: P31, L25-26: Regarding the sentence "In the absence of other toxicities, the toxicological significance of the alterations reported in some studies is unknown," the Reviewer suggests deleting this text and notes that "It is unclear what the authors are trying to conclude about the absence of data or the lack of agreement of across that are conducted exactly the same as to species, dose, route, duration, etc. The authors of this report are not in a position to make these after the fact judgments."

RESPONSE: *The text was deleted.*

COMMENT: P33, L7-16; P34, L1-7: The Reviewer notes: "In this paragraph start to describe the experimental animals in greater details; rats as albino rats or CD rats, dogs as beagle dog or beagles; hamsters as golden Syrian hamsters; rabbits as New Zealand white rabbits. Many of the studies cited are the same ones cited earlier. The author or authors should agree on their terminology and use one consistent set of terminology so as not to imply multiple studies when referring to only one."

RESPONSE: *There are no more details in the paragraphs identified by the Reviewer than in previous paragraphs from Chapter 3 of the profile. The strain of the animals tested is now provided throughout Section 3.2, Discussion of Health Effects by Route of Exposure.*

COMMENT: P38, L21: The Reviewer requests that when the gender of a child is known, it should always be added to the text and notes that based on a superficial count from the literature, there seems to be a tendency to females.

RESPONSE: *The comment refers to lack of alterations in liver function in a child following dermal intoxication with DEET described by Zadikoff (1979). The revised text states that the child was a girl.*

COMMENT: P38, L30: The Reviewer notes: "When expressing the dosing of 5 days/week for a total of 90/days, this is somewhat confusing…is it 90 days based on 7-day weeks (12weeks + 6 days) or on 5 days dosing (i.e., 18 weeks). Without getting the publication, the reader is left guessing. This confusion needs to be clarified. Suggest in all places where this study's dosing is mentioned to use the following format: '…1,000 mg/kg/day for 5 days/week for a total of 90 days onto the…'"

RESPONSE: *The comment refers to the sentence: "Application of up to 1,000 mg DEET/kg/day 5 days/week for 90 days onto the shaved back of pigs… (EPA 1992a)." The text was changed to "…5 days/week for 13 weeks…," which is how the study describes the dosing protocol. This change was done throughout the document.*

COMMENT: P44, L25-30: The Reviewer notes that it is confusing as to what studies are being referred to by terms such as "previous study," "more recent study," and the data in question and suggests that sentences be rewritten to clarify with specific data and references directly associated at all times.

RESPONSE: *The sentence was revised as follows: "…contrary to what was reported in a previous study (Abou-Donia et al. 2001b), in the more recent study (Abdel-Rahman et al. 2004), DEET was reported to statistically significantly increase (rather than have no effect) AChE activity in the cortex…" It is clear now what studies the words "previous" and "recent" refer to.*

COMMENT: P48, L10: The Reviewer notes that DEET dosing is expressed as microliters, but the concentration in this particular study is not given for the solution so the dose is unknown and requests an addition or clarification of details.

RESPONSE: *Only the concentration of the concentration of the DEET solutions tested was provided in the EPA (1990c) study. The volume of the DEET solution added to the incubation media (tissues dishes or coverslips) was not provided.*

COMMENT: P48, L22: The Reviewer suggests starting a new paragraph with the text "Dermal absorption of DEET..."

RESPONSE: *In the overview of Section 3.4, Toxicokinetics, ATSDR has tried to keep the information regarding absorption, distribution, metabolism, and excretion each in a separate paragraph. The paragraph regarding absorption is only eight lines. Therefore, ATSDR sees no reason to start a new paragraph, as suggested by the Reviewer.*

COMMENT: P48, L24-25: The Reviewer suggests changing the text to "…Because of the large number of the potential variables involved, the estimates are highly variable…"

RESPONSE: *The comment refers to the following sentence: "The rate and extent of dermal uptake are affected by species, sex, vehicle and/or formulation in which DEET is applied, dose, and evaporation rate; thus, estimates are highly variable." ATSDR sees no good reason to change the existing sentence, which details the factors involved in dermal absorption.*

COMMENT: P50, L2: The Reviewer suggests clarification because at a later point in this report, there is statement about the BSA and HAS data being from different studies where it is implied here that it is from the same study.

RESPONSE: *The BSA and HAS data are from different studies, as stated later in the document. The sentence in question in the overview does not imply either one or two studies. No change was made.*

COMMENT: P50, second paragraph: The Reviewer notes that species studied for metabolites are referred to in a vague manner as "humans and laboratory mammals" and "other species" and suggests that the authors consider making more specific references.

RESPONSE: *This is only an overview of Section 3.4.3, Metabolism. There is no need to be more specific in this paragraph.*

COMMENT: P53, L2-4: The Reviewer suggests deleting the following lines: "The application ….were not prevented."

RESPONSE: *The comment refers to the following sentence: "The application site was covered with a glass rectangular enclosure to minimize evaporative losses. In a study in which evaporative losses were not prevented, a peak plasma concentration of 0.3 μg DEET/mL was reached 90 minutes after the end of the 24-hour exposure (Fediuk et al. 2011)." ATSDR sees no reason to delete the text in question. It is important to specify whether or not the application site was covered so that estimates of the volatilization factor can be made.*

COMMENT: P53, L4: The Reviewer suggests changing the text to "…from the application site (Schoenig et al. 1996). A peak plasma concentration of…"

RESPONSE: *Because the text was not changed as a result of the previous comment, the current comment does not apply.*

COMMENT: P53, L10: The Reviewer questions which formulation had slower absorption.

RESPONSE: *Information was added indicating that absorption was lower for the formulation containing 7.5% DEET.*

COMMENT: P53: The Reviewer notes that the Qiu et al. (1997) reference doesn't indicate whether it is a or b.

RESPONSE: *This was changed to Qiu et al. (1997a).*

COMMENT: P54, L18: The Reviewer suggesting changing the text to "…When the DEET was applied…"

RESPONSE: *The comment refers to the following sentence: "When the repellent was applied alone, the concentration of DEET in the plasma peaked at ~28 μg/mL 2 hours after dosing, declined rapidly over the next 10 hours, and then declined very gradually for the subsequent 36 hours." DEET was not applied alone; it was applied with other substances in the repellent. The sentence is correct as it is. No changes were made.*

COMMENT: P59, L12: The Reviewer is not sure why the author of this report has not used standard scientific abbreviations for words that are used repetitively in the document and requests that this be done for intravenous, intraperitoneal, volume of distribution, half-life, etc.

RESPONSE: *As indicated previously, according to ATSDR's guidance, common terms such as intravenous, intraperitoneal, and others should not be abbreviated. Terms such as volume of distribution or half-life can be abbreviated if they appear repeatedly throughout the document. The profile was revised to comply with these general guidelines.*

COMMENT: P59, L25: The Reviewer requests that "starved" be defined (i.e., how many days these animals were not fed) and suggests that "fasted" is more often the term used in scientific publications.

RESPONSE: *The word "starved" was changed to "fasted." The revised text also indicates that the animals were fasted for 18–24 hours before treatment.*

COMMENT: P63, L11-13: The Reviewer questions whether there are methodology differences between these two studies.

RESPONSE: *The comment refers to the following sentence: "In contrast to the results reported by Schoenig et al. (1996), Taylor and Spooner (1990) detected unchanged DEET in the urine, accounting for 4.7–5.5% of the applied dose in the first 48 hours after dosing." There were slight differences in the analytical methods used; the Taylor and Spooner (1990) study lasted 48 hours, whereas the Schoenig et al. (1996) study lasted 7 days, and the applied doses were different: 100 versus 50 mg/kg.*

COMMENT: P64, L26: The Reviewer questions whether this refers to "mouse" or "treated mouse"?

RESPONSE: *The comment refers to the following sentence: "Usmani et al. (2002) also evaluated species differences in metabolism of DEET by human, rat, and mouse microsomes in vitro; the calculated intrinsic clearances of human and mouse microsomes were similar, while much higher clearance (>2-fold) was calculated from data in rat microsomes (Table 3-6)." The text refers to untreated mice; otherwise, it would have been specified.*

COMMENT: P67, L4: The Reviewer notes that abbreviations K_m and V_{max} are not in the appendix of acronyms.

RESPONSE: *As mentioned before, Appendix C is a standard list of terms of abbreviations, acronyms, and symbols that appears in all profiles. Definitions for K_m and V_{max} do not seem necessary, as readers of Section 3.4, Toxicokinetics, should be familiar with the meaning of these terms.*

COMMENT: P71, Section 3.4.4.4 Other Routes of Exposure: The Reviewer notes that there is variation in the references to beagles dogs (capitalization of Beagle varies between sections).

RESPONSE: *The document was revised for consistency of the word "Beagle".*

COMMENT: P71, Section 3.4.5: The Reviewer comments "This Section and Number of following Sections are bolded. There is no clear reason for this bolding. Why is this? Please explain."

RESPONSE: *Bolded sections are boilerplate text that appears in all draft toxicological profiles.*

COMMENT: P74, L15-19: The Reviewer notes: "Earlier it is implied that HAS and BSA binding data is in one study (see above) but here it is clearly a difference between two studies. Please clarify this disparity in report."

RESPONSE: *There is no disparity. The earlier text did not indicate that HAS and BSA binding data are from a single study.*

COMMENT: P77, L16: The Reviewer suggests changes to the text: "…when all biological systems will have fully developed…" and notes that this should be modified to reflect that the brain is not fully developed until the mid-20's.

RESPONSE: *The text that the Reviewer refers to is boilerplate text. ATSDR will consider the Reviewer's suggestion for future profiles.*

COMMENT: P78: The Reviewer suggests several editorial changes to the boilerplate text of Section 3.7, Children's Susceptibility.

RESPONSE: *ATSDR will consider the suggestions for future profiles.*

COMMENT: P79, L32: The Reviewer suggests changes to the text: "…9,086 human exposures…" and questions why the number differs from earlier.

RESPONSE: *The number 9,086 appears throughout the document. It has not changed in this section.*

COMMENT: P81, L8: The Reviewer suggests changes to the text: "…Several factors, however, can confound …"

RESPONSE: *The text in question is boilerplate text. No change was made.*

COMMENT: P83, L30: The Reviewer notes that reference(s) need to be added for the statement "Some investigators have…"

RESPONSE: *Abou-Donia et al. (1996) was added to the text.*

COMMENT: P84, L16: The Reviewer states that the abbreviation "PB" is missing from the Appendix for Acronyms.

RESPONSE: *As mentioned before, Appendix C is a standard list of terms of abbreviations, acronyms, and symbols that appears in all profiles.*

COMMENT: P84, L20: The Reviewer suggests changes to the text "DEET alone, PB plus DEET and all three compounds together did not affect ligand binding of nicotinic receptors in the cortex. A study that conducted…"

RESPONSE: *The sentence in question was changed as a result of a comment from another reviewer.*

COMMENT: P84, L23: *The Reviewer suggests changes to the text "*…combination showed that DEET alone, permethrin alone or the combination induced neuronal…"

RESPONSE: *The sentence in question was changed as a result of a comment from another reviewer.*

COMMENT: P87, L8: The Reviewer suggests changes to the text "Reasons *for this enhanced response* may include genetic makeup…"

RESPONSE: *The text in question is boilerplate text. No change was made.*

COMMENT: P95, L1: The Reviewer notes "Earlier the text read '…maternal blood and cord serum…' not 'maternal serum and cord…' Which is correct."

RESPONSE: *The text was changed to "maternal blood and cord serum."*

COMMENT: P97, L31: The Reviewer requests that the comma after "childhood" be deleted.

RESPONSE: *The text in question is boilerplate text. No change was made.*

CHAPTER 5

COMMENT: P104, L5: The Reviewer suggests changing the text to "….in the Toxics Release Inventory (TRI)…"

RESPONSE: *The change was made as suggested.*

COMMENT: P105, L5: The Reviewer notes that the reference is cited incorrectly and should be Weeks et al. (2012).

RESPONSE: *The change was made as suggested.*

CHAPTER 6

COMMENT: P107, L17: The Reviewer suggests changing the text to "…DEET, however, is considered…"

RESPONSE: *The change was made as suggested.*

COMMENT: P107, L29. The Reviewer notes that the TRI was abbreviation was defined earlier.

RESPONSE: *No changes were made; this is standard boilerplate text.*

COMMENT: P110, L24: The Reviewer suggests adding Keml (2010) to the reference list.

RESPONSE: *This reference was removed.*

COMMENT: P111, L24: The Reviewer suggests changing spelling of photo-oxidation.

RESPONSE: *No change was made; photooxidation is commonly used.*

COMMENT: P111, L32: The Reviewer suggests changing the text to "…considered to be hydrolytically stable; results from guideline studies, however, indicated…"

RESPONSE: *The change was made as suggested.*

COMMENT: P112, L5: The Reviewer suggests deleting the comma after "biodegradable."

RESPONSE: *The change was made as suggested.*

COMMENT: P112, L9: The Reviewer suggests changing the text to "…could be attributed to the toxic effects of DEET on microbial populations at high concentrations, such as those used in…"

RESPONSE: *The change was made as suggested.*

COMMENT: P112, L10-11: The Reviewer suggests changing the text to "…Testing indicated that DEET only caused minor ….activity and was not typically a concern…"

RESPONSE: *The change was made as suggested.*

COMMENT: P112, L14: The Reviewer suggests clarifying the term "fate process."

RESPONSE: *The beginning of Section 6.3, Environmental Fate was reworded to read: "The environmental fate of DEET, including the transport, partitioning, and transformation of this substance, is controlled by various physicochemical properties, degradation, and other loss processes."*

COMMENT: P112, L18: The Reviewer suggests changing the text to "Indirect photolysis in river water, however, resulted in…"

RESPONSE: *The change was made as suggested.*

COMMENT: P113, L8: The Reviewer suggests changing the text to "…were located; OECD guideline studies and aquifer studies, however, suggest…"

RESPONSE: *The change was made as suggested.*

COMMENT: P113, L15: The Reviewer suggests changing the text to "…Elimination rates were negligible in winter and spring months…"

RESPONSE: *The change was made as suggested.*

COMMENT: Page 113, line 34: The Reviewer suggests changing the text to "…with the membrane system; the other systems, however, removed DEET to…"

RESPONSE: *The change was made as suggested.*

COMMENT: P116, lL11: The Reviewer suggests changing the text to "In the 2000 United States Geological Survey (USGS), DEET...'

RESPONSE: *The change was made as suggested.*

COMMENT: P125, L: The Reviewer suggests changing the text to "…living in the Salinas Valley of California…"

RESPONSE: *The change was made as suggested.*

COMMENT: P130, L33: The Reviewer notes that repellent is spelled as "repellant."

RESPONSE: *All instances have been changed to repellent.*

COMMENT: The Reviewer noted that following a brief overview, several references do not appear to be cited in the body of the report.

RESPONSE: *The list of references provided was searched; citations were removed references if they were no longer cited in the draft.*

APPENDIX C

COMMENT: PC1-C5: The Reviewer notes that there are abbreviations used in the text of the report that are not included in Appendix C.

RESPONSE: *No changes were made; this is standard boilerplate text.*