DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR DI(2-ETHYLHEXYL)PHTHALATE (DEHP)

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

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

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ATSDR would like to thank these scientists for their review of the toxicological profile for DEHP. Depending on the nature of the comment, each Reviewer's comments have been divided into sections which could include General Comments, Specific Comments, ATSDR Charge Questions and Responses, and Annotated Comments. The Reviewer's exact comment is presented in plain text in the **COMMENT** field. ATSDR's response to each comment is presented in italics in the ***RESPONSE*** field. If the response included revised text from the toxicological profile, this appears indented under the response in plain text. The revised text is written in red font. Crossed-out red text indicates the word or words have been stricken from the document

Comments provided by Reviewer #1

ATSDR Charge Questions and Responses (Reviewer 1)

Chapter 1

QUESTION: Do you agree with those effects known to occur in humans as reported in the text? If not, provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

COMMENT: Yes, the data presented supported that.

RESPONSE: *No response is necessary.*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain.

COMMENT: Yes they appear to have been adequately described.

RESPONSE: *No response is necessary.*

QUESTION: Do you believe the derived intermediate inhalation MRL value is justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Do you believe the derived acute oral MRL value is justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Do you believe the derived intermediate oral MRL value is justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree that the data do not support derivation of acute inhalation, chronic inhalation, and chronic oral MRLs?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Chapter 2

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature for DEHP?

COMMENT: See below.

RESPONSE: *See responses below.*

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)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: Yes.

RESPONSE: *No response is necessary.*

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)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT: Yes, for the references noted.

RESPONSE: *No response is necessary.*

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?

COMMENT: Yes , there is variation of the response in various rodents and other mammals that is directly linked to the ability of the DEHP and metabolites to active the PPAR alpha receptor and induce the accepted mode of action . However the rodent species, rats and mice are the most studies and as such should be relied on the most.

RESPONSE: *No response is necessary.*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of Di(2-ethylhexyl)phthalate? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: Yes.

Effects of Di-2-ethylhexyl phthalate (DEHP) on gap-junctional intercellular communication (GJIC), DNA synthesis, and peroxisomal beta oxidation (PBOX) in rat, mouse, and hamster liver. Isenberg JS, Kamendulis LM, Smith JH, Ackley DC, Pugh G Jr, Lington AW, Klaunig JE. Toxicol Sci. 2000 Jul;56(1): 73-85.

Reversibility and persistence of di-2-ethylhexyl phthalate (DEHP)- and phenobarbital-induced hepatocellular changes in rodents. Isenberg JS, Kamendulis LM, Ackley DC, Smith JH, Pugh G Jr, Lington AW, McKee RH, Klaunig JE. Toxicol Sci. 2001 Dec;64(2): 192-9.

PPARalpha agonist-induced rodent tumors: modes of action and human relevance. Klaunig JE, Babich MA, Baetcke KP, Cook JC, Corton JC, David RM, DeLuca JG, Lai DY, McKee RH, Peters JM, Roberts RA, Fenner-Crisp PA. Crit Rev Toxicol. 2003;33(6): 655-780. Review

Mode of action framework analysis for receptor-mediated toxicity: The peroxisome proliferator-activated receptor alpha (PPARα) as a case study. Corton JC, Cunningham ML, Hummer BT, Lau C, Meek B, Peters JM, Popp JA, Rhomberg L, Seed J, Klaunig JE. Crit Rev Toxicol. 2014 Jan;44(1): 1-49. doi: 10.3109/10408444.2013.835784. Epub 2013 Nov 4. Review.

The PPARα-dependent rodent liver tumor response is not relevant to humans: addressing misconceptions. Corton JC, Peters JM, Klaunig JE.Arch Toxicol. 2018 Jan;92(1): 83-119. doi: 10.1007/s00204-017-2094-7. Epub 2017 Dec 2. Review.

RESPONSE: *For responses regarding Isenberg et al (2000, 2001) and Corton et al. (2018) please see responses following comments in which the Reviewer specifically requests inclusion of the studies in specific sections. Corton et al. (2014) was not added because Corton et al. (2018) is a more recent review on the same subject matter. Klaunig et al. (2003) was added as noted below. It was already cited in Section 3.1.6 (Animal-to-Human Extrapolation).*

Section 2.19, Cancer (Mechanisms of Hepatic Cancer): It is generally accepted that the PPARα MOA is not relevant to humans due to differences observed in key events downstream of PPARα activation (Corton et al. 2018; Klaunig et al. 2003; Maloney and Waxman 1999).

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for DEHP isomers?

COMMENT: No.

RESPONSE: *No response is necessary.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate

justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: They appear to be appropriate.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?

COMMENT: These are poorly defined terms and I would prefer they not be used. They are very qualitative. However if they are going to be used they need to be definitively defined every time they are used and must be included in the legend of the tables and figures in which these terms are used.

RESPONSE: *The definition of "less serious" and "serious" effects, along with discussion regarding professional judgement utilized to label effects as "less serious" versus "serious," can be found in introductory text at the beginning of Section 2.1:*

> Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.
>
> A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

Additionally, all effects associated with "less serious" and "serious" LOAELs are presented in the LSE tables for transparency. ATSDR will consider the Reviewer's suggestion regarding revised definitions of these terms in future versions of the profile guidance.

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain.

COMMENT: DEHP has been well documented to function through a ppar alpha mode of action (certainly for the liver effects). We know a lot about the role that the ppar alpha plays in toxicity and the differences in response in species. A recent paper by corton The PPARα-dependent rodent liver tumor

response is not relevant to humans: addressing misconceptions. Corton JC, Peters JM, Klaunig JE.Arch Toxicol. 2018 Jan;92(1): 83-119. doi: 10.1007/s00204-017-2094-7. Epub 2017 Dec 2. Review. Should be included and discussed int his document? Although it is not specifically dehp its appliacation involves all ppar alpha inducing compounds

RESPONSE: *An expanded discussion regarding PPARα-dependent rodent liver tumors was added to Section 2.19 Hepatic (Mechanisms of Hepatic Cancer).*

As discussed in Section 2.9, DEHP activates PPARα in rats and mice (Rusyn and Corton 2012). Therefore, it follows that observed liver tumors in rodents may be PPARα-dependent. Key events identified in this MOA are: (1) PPARα activation; (2) alterations in cell growth pathways; (3) perturbation of hepatocyte growth and survival; (4) selective clonal expansion of preneoplastic foci cells; and (5) increases in hepatocellular adenomas and carcinomas (apical event) (Corton et al. 2018). Isenberg et al. (2000, 2001) proposed that increased peroxisomal proliferation, increased replicative DNA synthesis, and inhibition of GJIC observed in rat and mouse livers following oral exposure to DEHP may contribute to PPARα-dependent hepatic tumor formation. Observed losses in GJIC following oral exposure to DEHP may permit unchecked proliferation of transformed cells. Inhibition of GJIC was not observed in exposed hamsters, a species that is refractory to PPARα-dependent tumors (Isenberg et al. 2000).

It is generally accepted that the PPARα mode of action is not relevant to humans due to differences observed in key events downstream of PPARα activation (Corton et al. 2018). Guyton et al. (2009) reported that PPARα activation may not be essential to rodent liver tumor formation since~~, as~~ liver tumors have been observed in some studies using PPARα-null mice ~~(reviewed by Guyton et al. 2009);~~ however, the validity of this argument has been questioned by Corton et al. (2018). Concerns regarding conclusions reached by Guyton et al. (2009) include: (1) all liver tumor types, including hepatoblastomas, which originate from a different cell population compared with adenomas and carcinomas, were combined for statistical analysis; (2) use of DEHP doses that did not cause liver tumors in wild-type mice in studies reporting tumors in PPARα-null mice; (3) comparison of findings in PPARα-null mice to non-concurrent controls of a different strain; and (4) different molecular environments in PPARα-null mice compared with wild-type mice (e.g., increased levels of background and DEHP-inducible levels of oxidative stress).

Peer review of Unpublished Studies

The updated DEHP profile includes seven unpublished studies.

1. CMA. 1984. Initial submission: A 21-day dose relationship study of di(2-ethylhexyl) phthalate in rats (project report) with cover sheets and letter dated 041492. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP. EPA Document No. 88-920002026. OTS053622. ttps: //ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0536220. July 18, 2017.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Did the study account for competing causes of death?

COMMENT: No deaths.

RESPONSE: *No response is necessary.*

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

COMMENT: This study was performed using the appropriate experimental approaches for the time and the data are valid.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

COMMENT: Yes.

RESPONSE: *No response is necessary*

2. Exxon Chemical Americas. 1990. An investigation of the effect of di-(2-ethylhexyl) phthalate on rat hepatic peroxisomes with cover letter. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA Document8691000007729. OTS0530399. TSCATS/414999.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Did the study account for competing causes of death?

COMMENT: No deaths reported.

RESPONSE: *No response is necessary.*

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

COMMENT: This study was performed using the appropriate experimental techniques.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

COMMENT: Yes.

RESPONSE: *No response is necessary*

3. ICI Amercas Inc. 1982. Bis(2-ethylhexyl)phthalate: A comparative subacute toxicity study in the rat and marmoset with cover letter dated 032283. Submitted to the U.S. Environmental Protection Agency under TSCA, Section 8DS. EPA878220040. OTS215194. TSCATS/020230.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Did the study account for competing causes of death?

COMMENT: No deaths reported.

RESPONSE: *No response is necessary.*

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

COMMENT: This study was performed using the appropriate experimental techniques.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

COMMENT: Yes.

RESPONSE: *No response is necessary.*

4. Myers BA. 1992a. A subchronic (4-week) dietary oral toxicity study of di(2-ethylhexyl)phthalate in B6C3F1 mice (final report) with attachments and cover letter dated 040392. Eastman Kodak Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA 86920000874. OTS 0535432. https: //ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0535432. October 14, 2016.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Did the study account for competing causes of death?

COMMENT: Yes the deaths were in the high dose group and discussion and documentation of the deaths was well done in the report.

RESPONSE: *No response is necessary.*

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

COMMENT: This study was performed using the appropriate experimental techniques.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

COMMENT: Yes.

RESPONSE: *No response is necessary.*

5. Myers BA. 1992b. Subchronic (13-week) dietary oral toxicity study of di(2-ethylhexyl)phthalate in Fischer 344 rats (final report) w-attachments and letter dated 040392 (missing pages 304 to 386). Eastman Kodak Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA 86920000875. OTS 0535433. https: //ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0535433. October 14, 2016.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Did the study account for competing causes of death?

COMMENT: No deaths reported, all rats survived until sampling.

RESPONSE: *No response is necessary.*

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

COMMENT: This study was performed using the appropriate experimental techniques.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

COMMENT: Yes.

RESPONSE: *No response is necessary.*

6. Pegg, DG. 1982. Disposition of di-2-ethylhexyl phthalate following inhalation and peroral exposure in rats. Washington, DC: General Motors Corp. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA86910000683. OTS0530339.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

COMMENT: Yes except it is unclear if untreated control animals were also used?.

RESPONSE: *Untreated controls are not required for toxicokinetic disposition studies (e.g., OECD 417).*

QUESTION: Did the study account for competing causes of death?

COMMENT: No deaths reported.

RESPONSE: *No response is necessary.*

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

COMMENT: This study was performed using the appropriate experimental techniques with the caveat that a description of the exposure and number of animals in the methods section could be improved.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

COMMENT: Yes.

RESPONSE: *No response is necessary.*

7. Schilling K, Deckardt K, Gembardt C, et al. 2001. Support: Di-2-ethylhexyl phthalate -two-generation reproduction toxicity study in Wistar rats continuous dietary administration, with cover letter dated 04/2/2001. Eastman Chemical Co. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. EPA89010000147. OTS0574025-1.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Did the study account for competing causes of death?

COMMENT: Yes the deaths were well described.

RESPONSE: *No response is necessary.*

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

COMMENT: This study was performed using the appropriate experimental techniques.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Chapter 3

Toxicokinetics

QUESTION: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

COMMENT: Yes the discussion was appropriate.

RESPONSE: *No response is necessary.*

QUESTION: Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Children and Other Populations that are Unusually Susceptible

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Please provide any relevant references.

COMMENT: No that I am aware of..

RESPONSE: *No response is necessary.*

QUESTION: Is there a discussion of populations at higher risk of susceptibility? Do you agree with the choice of populations? Please explain and provide any additional relevant references.

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Biomarkers of Exposure and Effect

QUESTION: Are the biomarkers of exposure specific for the substance? Please explain.

COMMENT: The biomarkers noted are appropriate.

RESPONSE: *No response is necessary.*

QUESTION: Are the biomarkers of effect specific for the substance? Please explain.

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Interactions with Other Chemicals

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? Please explain and provide any additional references.

COMMENT: Yes this was properly addressed

RESPONSE: *No response is necessary.*

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

COMMENT: The authors addressed this well.

RESPONSE: *No response is necessary.*

Chapter 4

QUESTION: Are any of the values or information provided in the chemical and physical properties tables wrong or missing? Please explain and provide any additional references.

COMMENT: The values appear correct and supported by the literature.

RESPONSE: *No response is necessary.*

QUESTION: Is information provided on the various forms of the substance? Please explain.

COMMENT: The information is correctly provided

RESPONSE: *No response is necessary.*

Chapter 5

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.

COMMENT: It is complete

RESPONSE: *No response is necessary.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT: The presentation is appropriate

RESPONSE: *No response is necessary.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT: The text covers these topics correctly. I am not aware of other infmation

RESPONSE: *No response is necessary.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the Substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT: Yes.

RESPONSE: *No response is necessary.*

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? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT: The sources and pathways are correctly descried and discussed. The population selected are appropriate

RESPONSE: *No response is necessary.*

Chapter 6

QUESTION: Do you know of other studies that may fill a data gap? Please provide any relevant references.

COMMENT: In a discussion of the liver effects and cancer effects of DEHP, several recent reviews should be included and discussed. these include:

> Mode of action framework analysis for receptor-mediated toxicity: The peroxisome proliferator-activated receptor alpha (PPARα) as a case study. Corton JC, Cunningham ML, Hummer BT, Lau C, Meek B, Peters JM, Popp JA, Rhomberg L, Seed J, Klaunig JE. Crit Rev Toxicol. 2014 Jan;44(1): 1-49. doi: 10.3109/10408444.2013.835784. Epub 2013 Nov 4. Review.
>
> The PPARα-dependent rodent liver tumor response is not relevant to humans: addressing misconceptions. Corton JC, Peters JM, Klaunig JE.Arch Toxicol. 2018 Jan;92(1): 83-119. doi: 10.1007/s00204-017-2094-7. Epub 2017 Dec 2. Review.

In addition, for some reason the Isenberg papers seem to be missing from the discussion of the topic

> Effects of Di-2-ethylhexyl phthalate (DEHP) on gap-junctional intercellular communication (GJIC), DNA synthesis, and peroxisomal beta oxidation (PBOX) in rat, mouse, and hamster liver. Isenberg JS, Kamendulis LM, Smith JH, Ackley DC, Pugh G Jr, Lington AW, Klaunig JE.Toxicol Sci. 2000 Jul;56(1): 73-85.

Reversibility and persistence of di-2-ethylhexyl phthalate (DEHP)- and phenobarbital-induced hepatocellular changes in rodents. Isenberg JS, Kamendulis LM, Ackley DC, Smith JH, Pugh G Jr, Lington AW, McKee RH, Klaunig JE. Toxicol Sci. 2001 Dec;64(2): 192-9.

RESPONSE: *Please see previous response regarding the expanded discussion of PPARa-mediated liver tumors in rodents in Section 2.19 (Mechanisms of Hepatic Cancer), including citations of Corton et al. (2018) and Isenberg et al. (2000, 2001). Corton et al. (2014) was not added because Corton et al. (2018) is a more recent review on the same subject matter.*

QUESTION: Do you agree with the identified data needs? Please explain.

COMMENT: This reviewer was not able to see a section detailing and describing data needs. There is some description (although very general) on data endpoints. This is an important issue and certainly understanding the mechanisms for the developmental, reproductive, pancreatic and leydig cell toxicity is important in understanding the relative toxicity and also the human relevance of the animal findings. This is a serious omission and should be addressed.

RESPONSE: *Data needs are discussed in Section 6.2; data needs for mechanistic data are specifically discussed in the "Health Effects" subsection of 6.2.*

QUESTION: Are the data needs presented in a neutral, non-judgemental fashion? Please note any bias in the text.

COMMENT: Inadequate discussion as noted above.

RESPONSE: *See response to comment above.*

Chapter 7

QUESTION: Are you aware of any additional regulations or guidelines that we should add? Please provide citations.

COMMENT: No.

RESPONSE: *No response is necessary.*

QUESTION: Are there any that should be removed? Please explain.

COMMENT: No.

RESPONSE: *No response is necessary.*

Appendix A – Minimal Risk Levels (MRLs)

Inhalation Acute MRL

QUESTION: Do you agree or disagree with the lack of an inhalation acute MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: Agree

RESPONSE: *No response is necessary.*

Inhalation Intermediate MRL

QUESTION: Do you agree or disagree with the proposed inhalation intermediate MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: Agree

RESPONSE: *No response is necessary.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose

COMMENT: Agree

RESPONSE: *No response is necessary.*

Inhalation Chronic MRL

QUESTION: Do you agree or disagree with the lack of an inhalation chronic MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: Agree

RESPONSE: *No response is necessary.*

Oral Acute MRL

QUESTION: Do you agree or disagree with the proposed oral acute MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: Agree

RESPONSE: *No response is necessary.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: Agree

RESPONSE: *No response is necessary.*

Oral Intermediate MRL

QUESTION: Do you agree or disagree with the proposed oral intermediate MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: Agree

RESPONSE: *No response is necessary.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: Agree

RESPONSE: *No response is necessary.*

Oral Chronic MRL

QUESTION: Do you agree or disagree with the lack of an oral chronic MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: Agree

RESPONSE: *No response is necessary.*

QUESTION: Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT: This section appears appropriate

RESPONSE: *No response is necessary.*

Appendix B – Literature Search Framework

QUESTION: Does Appendix B provide a sufficiently clear documentation of ATSDR's health effects literature search strategy and inclusion/exclusion criteria?

COMMENT: Yes

RESPONSE: *No response is necessary.*

QUESTION: Does it provide enough transparency regarding ATSDR's implementation of its inclusion and exclusion criteria (e.g., how ATSDR chose the studies it included in the health effects chapter)?

COMMENT: Yes

RESPONSE: *No response is necessary.*

Overall Usability of the Profile

QUESTION: Does the new chapter organization make it easier for you to find the information you need? For example, are you satisfied with the organization of the health effects chapter by organ system rather than exposure route?

COMMENT: YES, this seems to be easier to follow and certainly the tables are very improved over the past.

RESPONSE: *No response is necessary.*

QUESTION: Does the profile contain all of the information you need? If no, please elaborate on what additional information would be helpful.

COMMENT: Yes

RESPONSE: *No response is necessary*

QUESTION: If you have previously used any Toxicological Profile(s) for your work, which parts or content are the most useful to you, and what do you use it for?

COMMENT: Usually chapters 2 and 6.

RESPONSE: *No response is necessary.*

QUESTION: Are the new tables and figures clear and useful? Do they make the toxicological profile easier to read?

COMMENT: As noted above they are a significant improvement over the past presentation. They are much easier to follow and read.

RESPONSE: *No response is necessary.*

Annotated Comments (Reviewer 1)

COMMENT: Section 2.9 (Hepatic; Animal Studies – Elevated Liver Weight and Hypertrophy, Enzyme Induction, Peroxisomal Proliferation): these [PPAR alpha, CAR, PXR] are not hormone receptors they are nuclear receptors. This needs to be clarified here and throughout the document.

RESPONSE: *The term "nuclear hormone receptor" was changed to "nuclear receptor" in the two instances it was in the document.*

Section 2.1 (Introduction): . . . however, these responses are considered adaptive and human relevance is unclear due to association with the nuclear ~~hormone~~ receptors . . .

Section 2.9 (Hepatic): The European Society of Toxicologic Pathology (ESTP) convened an expert panel to define what constitutes an adverse hepatic effect and whether hepatic effects induced by nuclear ~~hormone~~ receptors such as PPARα, constitutive androstane receptor (CAR), or pregnane X receptor (PXR) are rodent-specific adaptive reactions; the findings of the panel are summarized by Hall et al. (2012).

COMMENT: Section 3.1.6 (Animal-to-Human Extrapolation): these two papers should be induced in the discussion of the animal to human extrabolation Mode of action framework analysis for receptor-mediated toxicity: The peroxisome proliferator-activated receptor alpha (PPARα) as a case study. Corton JC, Cunningham ML, Hummer BT, Lau C, Meek B, Peters JM, Popp JA, Rhomberg L, Seed J, Klaunig JE. Crit Rev Toxicol. 2014 Jan;44(1): 1-49. doi: 10.3109/10408444.2013.835784. Epub 2013 Nov 4. Review. The PPARα-dependent rodent liver tumor response is not relevant to humans: addressing misconceptions. Corton JC, Peters JM, Klaunig JE.Arch Toxicol. 2018 Jan;92(1): 83-119. doi: 10.1007/s00204-017-2094-7. Epub 2017 Dec 2. Review.

RESPONSE: *Corton et al. (2018) was added to the discussion regarding human relevance of effects mediated through PPARa. Corton et al. (2014) was not added because Corton et al. (2018) is a more recent review on the same subject matter.*

Some DEHP-induced effects in rats and mice are thought to be mediated through the peroxisome proliferator-activated receptor-alpha (PPARα) (e.g., liver effects) and it is generally agreed that humans and nonhuman primates are refractory, or at least less responsive than rodents, to PPARα-mediated effects (Corton et al. 2018; Klaunig et al. 2003; Maloney and Waxman 1999).

COMMENT: Section 6.3, Table 6-1 (Ongoing studies): The authors should check some of these studies and also the locations of the investigators For example Rita loch Caruso is at the univ of Michigan. This table should be redone and include the source of the information, the date of the studies (assuming they are grants) if the studies are in progress or completed and the source of the funding.

RESPONSE: *The source of the information (cited in the Footnotes for Table 6-1) was NIH RePORTER as this reports ongoing studies based on grants. The source of the funding is indicated in the last column of Table 6-1 (Sponsor column). ATSDR will consider revising Table 6-1 by including the date of the studies and changing the column heading of "Affiliation" to "Award Institution" in the future. The RePORTER search was updated for Draft 4 of the profile, and Table 6-1 was updated with information available as of October 4, 2018. Regarding Rita Loch Caruso, the award institution listed in RePORTER is still Northwestern University.*

Comments provided by Reviewer #2

ATSDR Charge Questions and Responses (Reviewer 2)

Chapter 1

QUESTION: Do you agree with those effects known to occur in humans as reported in the text? If not, provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

COMMENT: I have added a number of potential additional references as comments in the text and can send PDFs of the papers as needed. I agree with the general effects reviewed in Chapter 1.

RESPONSE: *Please see responses regarding suggested references in the Annotated Comments section below.*

QUESTION: Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

COMMENT: Potentially. As we know, rodents are not simply little humans and the species differ in many ways that may or may not impact how DEHP exposure affects health. That said, some of the seminal work on how DEHP exposure may impact human health were initially informed by findings in animal studies (e.g. Swan's work on prenatal phthalates and AGD). Thus when effects are observed in animals models there is reason for concern/caution until several well-designed, adequately powered studies suggest otherwise.

RESPONSE: *No response is necessary.*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain.

COMMENT: Yes, the description is adequate.

RESPONSE: *No response is necessary.*

QUESTION: Do you believe the derived intermediate inhalation MRL value is justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: For this as well as the other MRLs specified, they appear to be justifiable, however it is not totally apparent (based on the text) how the specific MRL was derived. Was there a formula applied based on the LOAEL? As an epidemiologist, not a toxicologist, a little more transparency in the calculation would be appreciated (or at least a reference to a paper describing that derivation). [I see that this is provided at the end of the document- perhaps a reference to how the MRLs were derived could be cited here.]

RESPONSE: *MRLs are presented in Chapter 1 for quick reference; however, details regarding how MRLs are derived and all calculations are included in Appendix A as now noted in a footnote for*

Table 1-1. ATSDR will consider the Reviewer's suggestion to include more details regarding MRL derivation in Chapter 1 in future versions of the profile guidance.

Table 1-1 (footnote): [a]See Appendix A for additional information.

QUESTION: Do you believe the derived acute oral MRL value is justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: See response to #4 [Charge question number 4 above].

RESPONSE: *See response above.*

QUESTION: Do you believe the derived intermediate oral MRL value is justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: See response to #4 [Charge question number 4 above].

RESPONSE: *See response above.*

QUESTION: Do you agree that the data do not support derivation of acute inhalation, chronic inhalation, and chronic oral MRLs?

COMMENT: Yes, it seems appropriate not to include those MRLs at this point and the explanation in the text is reasonable.

RESPONSE: *No response necessary.*

Chapter 2

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature for DEHP?

COMMENT: In general, yes. I think the conclusions as stated are conservative (for good reason in this type of document), but draw attention to the major organ systems that may be affected. It is not clear to me why the sections were ordered the way they were. For example the reproductive and developmental literatures are among the largest and strongest and yet they come after sections (like dermal and ocular) that cover very few studies and indicate very few effects. I had some specific comments on the reproductive and developmental sections (which are noted in the text).

As a general comment, if this is intended for a general readership, it might be worthwhile to add some text or a figure comparing doses used in the animal literature to estimates levels of human environmental and occupational exposure. This would help to unify the two literatures, I think, and put results in their proper context.

RESPONSE: *The order of the sections is standardized for all ATSDR profiles, and not determined by available data or strength of association. Responses to specific comments noted in the text are addressed in the Annotated Comments section below. Regarding the general comment, ATSDR will*

consider developing such a figure when the Guidance for Preparation of Toxicological Profiles goes through revision.

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)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: It would be helpful to have sample sizes included consistently – they are sometime omitted. There are some inherent issues with the human literature that are not discussed at length here, for instance the fact that most exposure assessment is based on a single spot sample (or perhaps 2-3 at best). On a related note, the issue of the duration of exposure is not raised in this section, but the point should be made that although DEHP has a short half-life in the body, exposure is virtually continuous because of the many sources (including diet). I wonder whether it might be worthwhile having a general section on limitations of exposure assessment in human studies.

RESPONSE: *The sample sizes are reported in the epidemiology tables under Population, and sample size is discussed in text when it is pertinent to comparisons among studies with differing results. Text was added to address the limitations in exposure estimates in the epidemiology literature.*

Section 2.1, Introduction: There are important limitations in the human epidemiological literature for DEHP. In particular, many of the epidemiological studies used a single spot urine sample to assess DEHP exposure. DEHP is rapidly metabolized and excreted, and urinary metabolite levels vary over time within an individual. Thus, a single urine sample may not correlate with long-term exposure patterns unless exposure levels remain very consistent. It is worth noting, however, that exposure to DEHP was probably relatively consistent for many years due to its ubiquitous presence in foods, packaging, and personal care products, until recent efforts to reduce or ban its use were initiated.

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)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT: I don't know the animal literature very well for most outcomes, so I am hoping that a toxicologist can provide more insight into the quality of the papers. I do feel that the authors did a good job of providing sufficient detail on the animal work (e.g. doses and timing, specific endpoints)

RESPONSE: *No response is necessary.*

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?

COMMENT: Same comment as above. That said, I don't think the issue of species needs to be belabored too much for the purposes of this report. The vast majority of studies on DEHP are in rats and mice, which is true of the biomedical literature more generally. As with most endpoints, non-human primates are arguably more relevant but cannot be widely used in research for many reasons. For certain specific endpoints other species may give insight (for instance guinea pigs for placental hormone production or voles for social behaviors) however I think that level of discussion goes beyond the scope of this report.

RESPONSE: *No response is necessary.*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of Di(2-ethylhexyl)phthalate? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: I have added several references in the comments.

RESPONSE: *Please see responses regarding suggested references in the Annotated Comments section below.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for DEHP isomers?

COMMENT: No.

RESPONSE: *No response is necessary.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: The NOAELs and LOAELs appear to be fine as presented.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?

COMMENT: While I might not have chosen that binary classification myself, the explanation is reasonable and I would agree with how the effects are presented in the table.

RESPONSE: *No response is necessary.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain.

COMMENT: Depending on how comprehensive you want to be, you might highlight the additional pathways of interest, particularly for the developmental section. For instance, activation of inflammatory/immune pathways could contribute to altered neurodevelopment. Similarly oxidative stress may play a role in many of the outcomes assessed and is mentioned only briefly. Studies on DEHP and oxidative stress are numerous including Ferguson et al (2015) EHP 123(3): 210-6; Ferguson et al (2017) Environ Health Perspect.125(3): 488-494.; Wu et al (2017) Environ Res. 153: 1-7.

RESPONSE: *The oxidative stress studies mentioned above (Ferguson et al. 2017, 2015; Wu et al. 2017) were added to Section 2.16 and/or Section 2.17 as indicated below. To further discuss oxidative stress and male reproductive toxicity, Huang et al. (2015b), Guo et al. (2014), and Zhang et al. (2016) were added to Section 2.16. To further discuss oxidative stress and inflammation, Ferguson et al. (2012, 2014a) studies were also added to Section 2.17.*

Section 2.16 (Mechanisms of Male Reproductive Toxicity): As discussed above, several studies suggest associations between diminished semen quality and DEHP metabolite levels in urine. Additionally, Zhang et al. (2006) reported an association between increased DEHP metabolite levels in semen and altered semen parameters (decreased semen volume, increased rate of sperm malformation). Some studies have indicated that oxidative stress may potentially be a mechanism of toxicity for observed alterations in male semen quality. In a study in PVC workers, increased urinary DEHP metabolite levels were associated with both decreased sperm quality and sperm ROS generation (Huang et al. 2014b). Other studies reported associations between urinary DEHP metabolite levels and urinary markers of oxidative stress (e.g., 8-hydroxy-2'-deoxyguanosine [8-OHdG], isoprostane, carnitines) in couples planning to become pregnant (Guo et al. 2014), couples seeking fertility treatment (Wu et al. 2017), and men from a fertility cohort (Zhang et al. 2016); however, these studies do not have concurrent evaluations of male reproductive parameters. Direct damage to sperm DNA may also underlie observed male reproductive effects, as increased urinary levels of DEHP metabolites were associated with DNA damage in men from a fertility cohort (Hauser et al. 2007).

Section 2.16 (Epidemiology Studies—Pregnancy Outcomes): Ferguson et al. (2014a) proposed that increased risk of preterm birth may be associated with pro-inflammatory activities of DEHP based on positive associations between DEHP exposure and systemic markers of inflammation and oxidative stress (Ferguson et al. 2012). In support of this proposed mechanism, follow-up studies in this birth cohort showed a positive association between maternal urinary levels of DEHP metabolites and urinary levels of the oxidative stress marker 8-isoprostane (Ferguson et al. 2015). Additionally, the association between urinary DEHP metabolites and spontaneous preterm birth was mediated by maternal urinary levels of 8-isoprostane using complex regression models (Ferguson et al. 2017).

Section 2.17 (Mechanisms of Neurodevelopmental Toxicity): Observed DEHP-moderated alterations in oxidative stress and inflammatory pathways (Ferguson 2017, 2015, 2012; Wu et al. 2017) could potentially contribute to neurodevelopmental toxicity of DEHP; however, the potential role(s) of these pathways has not been specifically evaluated with regard to neurodevelopment.

Peer review of Unpublished Studies

QUESTION: The updated Di(2-ethylhexyl)phthalate profile includes seven unpublished study(ies) by

CMA. 1984. Initial submission: A 21-day dose relationship study of di(2-ethylhexyl) phthalate in rats (project report) with cover sheets and letter dated 041492. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP. EPA Document No. 88-920002026. OTS053622. https: //ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0536220. July 18, 2017.

Exxon Chemical Americas. 1990. An investigation of the effect of di-(2-ethylhexyl) phthalate on rat hepatic peroxisomes with cover letter. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA Document8691000007729. OTS0530399. TSCATS/414999.

ICI Amercas Inc. 1982. Bis(2-ethylhexyl)phthalate: A comparative subacute toxicity study in the rat and marmoset with cover letter dated 032283. Submitted to the U.S. Environmental Protection Agency under TSCA, Section 8DS. EPA878220040. OTS215194. TSCATS/020230.

Myers BA. 1992a. A subchronic (4-week) dietary oral toxicity study of di(2-ethylhexyl)phthalate in B6C3F1 mice (final report) with attachments and cover letter dated 040392. Eastman Kodak Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA 86920000874. OTS 0535432. https: //ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0535432. October 14, 2016.

Myers BA. 1992b. Subchronic (13-week) dietary oral toxicity study of di(2-ethylhexyl)phthalate in Fischer 344 rats (final report) w-attachments and letter dated 040392 (missing pages 304 to 386). Eastman Kodak Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA 86920000875. OTS 0535433. https: //ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0535433. October 14, 2016.

Pegg, DG. 1982. Disposition of di-2-ethylhexyl phthalate following inhalation and peroral exposure in rats. Washington, DC: General Motors Corp. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA86910000683. OTS0530339.

Schilling K, Deckardt K, Gembardt C, et al. 2001. Support: Di-2-ethylhexyl phthalate -two-generation reproduction toxicity study in Wistar rats continuous dietary administration, with cover letter dated 04/2/2001. Eastman Chemical Co. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. EPA89010000147. OTS0574025-1.

These studies containing 302 pages of text were unavailable to ATSDR when preparing the original profile. Please comment on the quality of the study, namely:

- Did the study use an adequate number of animals and practice good animal care?
- Did the study account for competing causes of death?
- Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?
- If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.
- Do you agree with the conclusions of the author? If not, please explain.

COMMENT: As an epidemiologist, not a toxicologist, I do not feel qualified to review the methods used in these papers. However, as a general rule, I think it would be a mistake to include data from industry-sponsored studies that were not published in peer reviewed journals, The authors of the DEHP profile have done considerable work to review the large published literature and the inclusion of 7 unpublished reports seems out of line with the rigorous selection process used throughout the rest of the report and could undermine that effort at fair and responsible coverage.

RESPONSE: *In order to be as comprehensive as possible and to avoid reporting bias, it is standard ATSDR protocol to evaluate relevant reports from the grey literature including unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, plus theses and dissertations (as outlined in Appendix B). To ensure fair and responsible coverage, non-peer-reviewed studies that are considered relevant to the assessment of the health effects undergo peer review by at least three ATSDR-selected experts who have been screened for conflict of interest.*

Chapter 3

Toxicokinetics

QUESTION: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

COMMENT: This section appears fairly comprehensive- no additions suggested.

RESPONSE: *No response is necessary.*

QUESTION: Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

COMMENT: The models and data presented are adequate.

RESPONSE: *No response is necessary.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT: The section devoted to this topic is fairly limited, though there is additional text in the chapter that is relevant to the discussion. No citations are provided for the first paragraph in this section (p. 265).

RESPONSE: *Section 3.1.6, Animal-to-Human Extrapolations, was expanded to include additional relevant details regarding toxicokinetics and potential species differences. Citations and/or referral to where references could be found were added. See below.*

> The toxicokinetics of DEHP in humans are generally similar to those that have been observed in monkeys, rats, mice, hamsters, and guinea pigs. As discussed in Section 3.1.1, oral absorption data indicate absorption of 11–70% in humans and 30–78% in laboratory animals. No reliable data are available regarding distribution in humans. Metabolic pathways are similar between species (Figure 3-1), although species differences in relative abundance of metabolites and glucuronide conjugates have been reported. Extensive oxidative metabolism of MEHP was demonstrated to occur in rats compared to humans, and metabolites were primarily unconjugated in rat urine, whereas conjugation with glucuronide was extensive in humans (Albro et al. 1982a); see Section 3.1.3 for additional details. Species differences in DEHP hydrolase activities have been reported with much lower activities in human and marmoset liver tissue compared with rodent liver tissue (Ito et al. 2005, 2014). In both humans and laboratory animals, elimination is primary via excretion in urine and feces (Daniel and Bratt 1974; Koch et al. 2004, 2005a; Kurata et al. 2012a, 2012b). Elimination half-lives for DEHP and MEHP did not differ widely between ~~across~~ species (Table 3-5).

Children and Other Populations that are Unusually Susceptible

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Please provide any relevant references.

COMMENT: Given that the Chapter 2 section on developmental effects is pretty thorough, I would not suggest any additions here.

RESPONSE: *No response is necessary.*

QUESTION: Is there a discussion of populations at higher risk of susceptibility? Do you agree with the choice of populations? Please explain and provide any additional relevant references.

COMMENT: I am satisfied with the populations discussed.

RESPONSE: *No response is necessary.*

Biomarkers of Exposure and Effect

QUESTION: Are the biomarkers of exposure specific for the substance? Please explain.

COMMENT: Yes and this section is well written, raising many of the main issues with exposure assessment. I've added one need for clarification in the text.

RESPONSE: *Please see response regarding text clarification in the Annotated Comments section below.*

QUESTION: Are the biomarkers of effect specific for the substance? Please explain.

COMMENT: N/A. None noted.

RESPONSE: *No response is necessary.*

Interactions with Other Chemicals

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? Please explain and provide any additional references.

COMMENT: Although the animal literature is reviewed thoroughly, there is little discussion of any work on this in humans. It seems worth stating that there is no work on this topic in humans (if that is the case). There is no discussion of hazardous waste sites, moreover, but I don't think it would be a particularly relevant addition and know of no literature on the topic.

RESPONSE: *A statement was added to the beginning of Section 3.4 noting the lack of human data on interactions.*

> Section 3.4 (Interactions With Other Chemicals): There are no studies in humans examining interactions between DEHP and other chemicals; however, most available human studies examine members of the general population with potential exposures to other phthalates as well as other ubiquitous chemicals.

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

COMMENT: Discussion of this is limited, but I am not aware of any additional relevant literature.

RESPONSE: *No response is necessary.*

Chapter 4

QUESTION: Are any of the values or information provided in the chemical and physical properties tables wrong or missing? Please explain and provide any additional references.

COMMENT: To the best of my knowledge, the information provided is correct.

RESPONSE: *No response is necessary.*

QUESTION: Is information provided on the various forms of the substance? Please explain.

COMMENT: I am not sure what this question means in the context of DEHP.

RESPONSE: *No response is necessary.*

Chapter 5

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.

COMMENT: Acknowledging that some relevant data is missing or incomplete because it is unavailable (for instance a comprehensive survey of DEHP production in the US), the information provided is adequate.

RESPONSE: *No response is necessary.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT: Yes- the authors have done a good job of describing this process. No additional information to add.

RESPONSE: *No response is necessary.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT: Nothing to add.

RESPONSE: *No response is necessary.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the Substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT: The text makes clear there are considerable concerns and limitations relative to measured levels of DEHP in the environment, particularly water samples, and provides adequate data.

RESPONSE: *No response is necessary.*

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? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT: Yes, I would suggest re-emphasing here that food is the main source as that point is lost when a long list of other sources is discussed as well (for example on p. 206). The potential high exposure populations are well covered.

RESPONSE: *It is not clear where the Reviewer would like this emphasis to occur. The referred page (p. 206) is in Section 2.17, discussing male reproductive effects in animals. In Chapter 5, this is addressed in Section 5.6 in the following statement: "The predominant source of DEHP exposure to the general population by the oral route is through the diet (Doull et al. 1999; Gong et al. 2014; Huber et al. 1996; NTP 2000). Clark et al. (2011) reported that ingestion of food accounts for approximately 95% of total exposure for the toddler through adult age range. Food reviews in Europe concluded that the most important route of exposure to DEHP for the general population is via food, which was reported to account for 80 to >90% of the daily intake of DEHP in adults (Erythropel 2014)." No changes were made to the profile in response to this comment.*

Chapter 6

QUESTIONS: Do you know of other studies that may fill a data gap? Please provide any relevant references. Do you agree with the identified data needs? Please explain. Are the data needs presented in a neutral, non-judgemental fashion? Please note any bias in the text.

COMMENT: It may be worth repeating here that the literature was not comprehensively reviewed in chapter 2 thus the summary figures have some limitations and should not be considered totally comprehensive. I also think it would be useful to break the developmental section down further into subcategories (e.g. neurodevelopment, birth outcomes, body size/growth). Similarly the reproductive section might be broken into male and female. These two represent the largest number of studies and aggregate a wide range of outcomes (particularly the developmental category).

RESPONSE: *The text below was added to Section 6.1 (Information on Health Effects) to indicate that the figure may not be inclusive of the entire body of literature. Additionally, the footnote in Figure 6-1 was revised to indicate that it included only studies discussed in Chapter 2. The body/organ systems were*

not further broken down into subcategories because Figure 6-1 is a template figure used in all toxicological profiles developed under current guidance. ATSDR will consider the Reviewer's suggestion to include subcategories in Figure 6-1 (where appropriate) in future versions of the profile guidance.

As noted in Section 2.1, both human and animal data were prioritized due to the extensive number of human and animal studies. Therefore, Figure 6-1 is not inclusive of the entire body of literature. The criteria for study prioritization are further discussed in Appendix B. The purpose of this figure is to illustrate the information concerning the health effects of DEHP.

Figure 6-1 (footnote): *Includes only studies discussed in Chapter 2; the number of studies include those finding no effect; most studies examined multiple endpoints.

Chapter 7

QUESTIONS: Are you aware of any additional regulations or guidelines that we should add? Please provide citations. Are there any that should be removed? Please explain.

COMMENT: No comment by reviewer.

RESPONSE: *No response is necessary.*

Appendix A – Minimal Risk Levels (MRLs)

Inhalation Acute MRL

QUESTION: Do you agree or disagree with the lack of an inhalation acute MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: I agree that the results of the two studies discussed are not sufficient to establish an inhalation acute MRL.

RESPONSE: *No response is necessary.*

Inhalation Intermediate MRL

QUESTION: Do you agree or disagree with the proposed inhalation intermediate MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: This MRL seems reasonable and justified based on the studies discussed.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose

COMMENT: I am not sufficiently familiar with establishing MRLs to evaluate this, but if these uncertainty factors are well established and widely used for other similar types of exposure, this seems to be a reasonable approach. If there is an appropriate citation to explain those choices, it could be added.

RESPONSE: *MRLs were derived using standard protocols as published in the following reference: Chou CH, Holler J, De Rosa CT. 1998. Minimal risk levels (MRLs) for hazardous substances. J Clean Technol Environ Toxicol Occup Med 7(1):1-24. Additional details may be found at: https://www.atsdr.cdc.gov/mrls/index.asp and a compendium of MRL papers are available at: https://www.atsdr.cdc.gov/mrls/compendium_of_papers_on_mrls_and_health_effects.html.*

Inhalation Chronic MRL

QUESTION: Do you agree or disagree with the lack of an inhalation chronic MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: I agree given that there appears to be no basis on which to estimate an MRL.

RESPONSE: *No response is necessary.*

Oral Acute MRL

QUESTION: Do you agree or disagree with the proposed oral acute MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: This appears to be reasonable and the process used to specify this MRL is well described.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: The explanation for why an uncertainty factor of 3 rather than a 10 was used for human variability is not totally clear based on the explanation provided. Otherwise it looks reasonable.

RESPONSE: *The default UF of 10 for human variability is designed to make sure derived values are protective of the general population as well as susceptible populations. It is standard procedure to decrease this UF from 10 to 3 if the point of departure is based on a critical effect in a susceptible population (in this case, exposure during early development). A partial UF of 3 is still used because it is not known if the developing fetus is the most susceptible population. The explanation provided "a full-factor of 10 was not warranted because the study population (F1 offspring exposed in utero) is considered a susceptible subpopulation since offspring are not fully developed until after puberty (or later)" is standard ATSDR language for this scenario.*

Oral Intermediate MRL

QUESTION: Do you agree or disagree with the proposed oral intermediate MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: This appears to be reasonable and the process used to specify this MRL is well described.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: The explanation for why an uncertainty factor of 3 rather than a 10 was used for human variability is not totally clear based on the explanation provided. Otherwise it looks reasonable.

RESPONSE: *See response to this issue in the Oral Acute MRL section above.*

Oral Chronic MRL

QUESTION: Do you agree or disagree with the lack of an oral chronic MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: This seems like a conservative and appropriate approach given the relevant findings and potential risks to the developing fetus.

RESPONSE: *No response is necessary.*

QUESTION: Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT: No additional comments.

RESPONSE: *No response is necessary.*

Appendix B – Literature Search Framework

QUESTION: Does Appendix B provide a sufficiently clear documentation of ATSDR's health effects literature search strategy and inclusion/exclusion criteria?

COMMENT: Yes, extremely clear and thorough. I am unclear as to how the seven unpublished studies that the external reviewers were asked to consider fit into this. It does not appear that they came from any of the sources specified and stand out from the rest of the literature in that they were not published in peer reviewed journals.

RESPONSE: *Table B-3 in Appendix B shows strategies used to augment the literature search to include reports not published in peer-reviewed journals. It is standard ATSDR protocol to evaluate relevant reports from the grey literature including unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations (https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf). As discussed in a previous comment, unpublished papers with relevant information included in the profile undergo peer review by at least three ATSDR-selected experts who have been screened for conflict of interest.*

QUESTION: Does it provide enough transparency regarding ATSDR's implementation of its inclusion and exclusion criteria (e.g., how ATSDR chose the studies it included in the health effects chapter)?

COMMENT: Yes, excellent job. Where are the epidemiological studies represented in Figure B-1? If it is only the animal literature, the title should specify that.

RESPONSE: *Figure B-1 is inclusive of all studies cited in the ATSDR profile, including epidemiological studies. A heading was added to the text referring to Figure B-1 for clarity, as its location following the heading "Prioritization of Animal Data" could lead to the misinterpretation that it was exclusively for animal data.*

> Appendix B: ***Summary of Literature Search and Screening***. A summary of the results of the literature search and screening for the DEHP profile is presented in Figure B-1.

Overall Usability of the Profile

QUESTION: Does the new chapter organization make it easier for you to find the information you need? For example, are you satisfied with the organization of the health effects chapter by organ system rather than exposure route?

COMMENT: In general, yes, the information is relatively easy to find and the organization makes sense. The only part that I question is the aggregation of "developmental" effects into one category when they really span many organ systems and are arguably the most robust part of the literature. If that organization is preferred by the authors, I think it would be useful to have a section in chapter 1 explaining that all of the organ system results are specific to adults (or postnatal exposures) and any studies examining prenatal exposures will be found under "developmental". For instance a study looking at prenatal DEHP exposure and semen quality would be under developmental, not reproductive, even though the endpoint is clearly reproductive.

RESPONSE: *ATSDR considers any health effect associated with early life exposure a developmental effect. Text in Sections 1.2 and 2.1 was revised to further clarify this point.*

> Section 1.2: In oral animal studies, effects consistently reported at low doses (≤50 mg/kg/day) include altered development or function of several systems following *in utero* and/or early life exposure (i.e., developmental effects), altered immune responses, ~~altered glucose homeostasis,~~ damage to the sexually mature male reproductive system, renal effects, and ~~renal and~~ hepatic effects (see **Error! Reference source not found.**). Effects on body weight and the neurological, hematological, sexually mature female reproductive, and non-reproductive endocrine systems were observed at higher DEHP doses.
>
> Section 2.1: Data presented under individual organ systems are specific to post-pubertal adult animals, while studies evaluating effects following prenatal or early life (pre-pubertal) exposures are considered developmental.

QUESTION: Does the profile contain all of the information you need? If no, please elaborate on what additional information would be helpful.

COMMENT: Please see comments on section 2 about adding text or a figure comparing doses used in the animal literature to typical human levels of exposure.

RESPONSE: *Please see response in Section 2.*

QUESTION: If you have previously used any Toxicological Profile(s) for your work, which parts or content are the most useful to you, and what do you use it for?

COMMENT: Yes, I sometimes use them as reference guides when trying to learn about an unfamiliar chemical or some aspect of exposure with which I am unfamiliar. I also reference the profiles in manuscripts and grants on occasion. I tend to focus most on the literature review of overall health effects.

RESPONSE: *No response is necessary.*

QUESTION: Are the new tables and figures clear and useful? Do they make the toxicological profile easier to read?

COMMENT: The figures are good and mostly easy to understand. Will the full figure legend info (pp. C3-4) go alongside the figures in the main text?

RESPONSE: *The lengthy text on pp. C3-4 is not included alongside the figures in the main text. ATSDR will consider the Reviewer's suggestions in future revisions of the profile guidance.*

Annotated Comments (Reviewer 2)

COMMENT: Section 1.1: Small point, but the items listed in the subsequent sentence under "for instance" are not toys.

RESPONSE: *The text was revised for accuracy, as shown below.*

> Because of concerns regarding potential health effects from DEHP exposure, many ~~toy~~ manufacturers have discontinued use of DEHP in their products. For instance, the use of DEHP has also been discontinued in domestically produced baby teethers, rattles, and most food packaging products (CDC 2016; CPSC 1999; Wilkinson and Lamb 1999).

COMMENT: Section 1.1: There is evidence from NHANES as well as epidemiological studies that levels of DEHP metabolites have been dropping over the past two decades as DEHP is phased out of some products**.**

RESPONSE: *The trend toward decreased DEHP exposure based on NHANES data was added to Section 1.1.*

> In support, the National Health and Nutrition Examination Survey (NHANES) data show an overall decrease in urinary levels for all DEHP metabolites by approximately 2-fold or greater between 1999 and 2014 for a broad mix of the general public (CDC 2018; CPSIA 2008).

COMMENT: Section 1.2: This is a little misleading as not all of the esters appear to have similar health impacts. For instance while DEHP may be anti-androgenic, there is not much evidence that DEP is.

RESPONSE: *The text was revised for clarity.*

> Many ~~These~~ phthalates have similar effects.

COMMENT: Section 1.2: Not totally clear what you mean here given that the first part of the sentence is specific to DEHP in particular (not evaluating health effects of various esters).

RESPONSE: *The sentence was edited for clarity.*

Thus, ~~the data available from~~ human epidemiology studies evaluating potential adverse effects from exposure to phthalates (including DEHP) ~~of humans exposed to DEHP~~ are insufficient to draw firm conclusions regarding cause and effect or dose-response for individual phthalate esters.

COMMENT: Section 1.2 (Summary of Health Effects), bulleted list of primary health effects, developmental: I find this categorization to be a little tricky because this represents a huge literature that captures the same endpoints as discussed elsewhere (reproductive, endocrine, etc…) so it often doesn't seem like it should be segregated out. One alternative option would be that for each body system, there are subsections on prenatal and adult/postnatal exposures.

RESPONSE: *The bullet was adapted by removing text.*

Developmental effects (altered glucose homeostasis and impaired development/function of the reproductive, renal, hepatic, and nervous systems ~~with early life exposure~~)

According to ATSDR guidance, any health effect associated with exclusively early life exposure (prior to sexual maturity) a developmental effect. The guidance can be found here: https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf.

Furthermore, ATSDR addresses this by directing the reader of organ-specific effects to the developmental section, 2.17. This direction occurred in hepatic, renal, neurological, reproductive, and noncancer endpoints. Alternatively, data are discussed alongside adult data (respiratory, cardiovascular, endocrine, immunological). In this case, the availability of these data are mentioned briefly in Section 2.17, and the reader is directed to organ-specific sections.

COMMENT: Section 2.1, Health Effects Introduction, bulleted list of primary health effects, reproductive: [re: "Available studies on fertility effects in humans are limited, but do not indicate an association between DEHP exposure and infertility"]: Is this conclusion based on only one study (Buck Louis et al 2014)? If so, I might just leave the sentence as "Available studies on fertility effects in humans are limited."

RESPONSE: *The statement was revised as shown below.*

Available studies on fertility effects in humans are limited to a single study in 439 couples~~, but~~ and do not indicate an association between DEHP exposure and infertility.

COMMENT: Figure 2-2. Perhaps add something to the legend indicating that the number in the figure refers to the chart above.

RESPONSE*: The legends for Table 2-1 and Table 2-2 indicate that the column "Figure key" contains the number corresponding to entries in Figure 2-2 and Figure 2-3, respectively. This is consistent with the User's Guide in Appendix C. ATSDR will consider the Reviewer's suggestion regarding figure legends in future versions of the profile guidance.*

COMMENT: Section 2.3, Body Weight, Epidemiology Studies [re: "The epidemiological data on DEHP metabolite levels and obesity parameters may be confounded by correlations among body weight,

caloric intake, urinary creatinine levels, and DEHP exposure"]: Also potentially dietary composition as levels may be higher in processed and fast foods that are themselves obesogenic

RESPONSE: *This potential confounder was added to the profile.*

The epidemiological data on DEHP metabolite levels and obesity parameters may be confounded by ~~correlations~~covariation among body weight, caloric intake, dietary composition (e.g., processed versus unprocessed foods), urinary creatinine levels, and DEHP exposure.

COMMENT: Section 2.3, Body Weight, Epidemiology Studies: The human literature on prenatal exposures and offspring body size is considered elsewhere?

RESPONSE: *Yes; these are addressed in Section 2.17 (Developmental). The following statement was added to Section 2.3 (Overview) for clarification:*

Studies evaluating weight after developmental exposure (e.g., birth weight) are discussed in Section 2.17 (Developmental).

COMMENT: Section 2.3, Body Weight, Mechanisms of Obesity [re: "Kim and Park (2014) also suggested that reduced birth weight in rodents exposed gestationally to DEHP may lead to a compensatory increase in the uptake of nutrients resulting in obesity later in life."]: This speaks to my confusion about segregating developmental effects. Why is this developmental hypothesis included here but none of the developmental literature? For instance:

Harley et al (2017) Pediatr Res. 2017 Sep;82(3): 405-415. doi: 10.1038/pr.2017.112. Epub 2017 May 31.
Buckley et al (2016) Epidemiology. 2016 May;27(3): 449-58.
Buckley et al (2016) Environ Health Perspect. 2016 Apr;124(4): 507-13.phtha

Similarly I didn't see anything on gestational weight gain. For example: Bellavia et al (2017) nt J Hyg Environ Health. 2017 Nov;220(8): 1347-1355.

RESPONSE: *The Kim and Park study (2014) was deleted as it did not belong in the body weight section of the profile and there are no mechanistic data to support the hypothesis suggested.*

The two Buckley papers (2016a, 2016b) were already a part of the toxicological profile text in Section 2.17, Developmental. Citations for these appear as follows: Table 2-14 and "Generally, the associations between maternal metabolite levels and BMI, waist circumference, and percent fat mass were negative (i.e., higher DEHP exposure was associated with lower BMI, waist circumference, and percent fat mass; Agay-Shay et al. 2015; Buckley et al. 2016a; 2016b …" Data pertaining to Bellavia et al. (2017) and Harley et al. (2017) were added to Tables 2-4 and 2-14, respectively. Relevant information from Bellavia et al. (2017) was added to Section 2.3. Relevant information from Harley et al. (2017) was added to Section 2.17. The edits and additions below were added to clarify or include studies.

Section 2.3 (Body Weight, Epidemiology Studies): Studies published after Goodman et al. (2014) that met inclusion criteria (see Appendix B) are shown in Table 2-4; these include ~~one~~ a cohort study (Teitelbaum et al. 2012) ~~in which~~ where exposure was measured approximately 1 year prior to anthropometric measurements; a cohort study (Bellavia et al. 2017) where exposure was measured in pregnant women during the first trimester and body weights were measured at first and second trimester visits; and ~~eight~~ nine cross-sectional or case-control studies~~, in which~~ that measured exposure and outcome ~~were measured~~ at the same time. Six additional cohort studies evaluating potential associations between growth or obesity parameters

in children and prenatal exposure (maternal urinary metabolites) are discussed in Section 2.17 (Developmental), as this study design evaluates potential effects of exposure during early development. Teitelbaum et al. (2012) observed no association between DEHP metabolite levels in the urine of 7-year-old children and BMI or waist circumference in the children at age 8 years. Bellavia et al. (2017) observed an inverse U-shaped relationship between first trimester urinary ∑DEHP metabolite levels and early gestational weight gain (between first and second trimesters) in a cohort of pregnant women with full-term births in a prospective analysis. In a cross-sectional analysis of the same cohort, urinary ∑DEHP metabolite levels were associated with higher first trimester BMI (Bellavia et al. 2017).

Section 2.17 (Developmental, Birth Size and Growth): In contrast to the other studies, Harley et al. (2017) reported increased odds (Table 2-14) of being overweight or obese at 12 years of age when DEHP metabolite levels were doubled in maternal urine; however, sensitivity analysis indicated that maternal BMI influenced these results. A positive association was also reported between waist circumference z-score and maternal urinary DEHP levels at 5 years of age, but not at 7–12 years (Harley et al. 2017). No associations were observed between BMI z-score at 5–12 years or percent body fat at 9–12 years and maternal urinary DEHP levels.

COMMENT: Section 2.4, Respiratory, Epidemiology Studies [re: "Kolena et al. (2014) observed improved pulmonary function (FEV1/FVC) with higher urinary MEHP levels (mean 15 ng/mL) in a study of 30 community service workers . . ."]: This sample size seems very small – not sure it makes sense to include.

RESPONSE: *The study was included because it met the defined inclusion criteria for human studies described in Appendix B. The statement, below, regarding the limitation due to sample size was added.*

Interpretation of this study is limited by small sample size.

COMMENT: Section 2.4, Respiratory, Animal Studies: So should this be classified as a developmental study rather than respiratory?

RESPONSE: *Please refer to the Section 1.2 response about overlapping health effect endpoints and their locations and citations to different toxicological profile sections. Yes, the Chen et al. (2010) study is classified as developmental for offspring endpoints and this is indicated in Table 2-2 and Section 2.17 (Developmental, Animal Studies- Other Developmental Effects) referring reader back to Section 2.4 (Respiratory). Chen et al. (2010) is the only developmental study with pulmonary effects findings, so it is only discussed in the respiratory section. The text was clarified as shown below.*

In ~~laboratory animals~~a developmental study, altered lung structure has been reported in PND 1 and 21 offspring of rats exposed to DEHP at gavage doses of 750 mg/kg/day from GD 12 to PND 0 or from GD 12 to PND 21, respectively (Chen et al. 2010).

COMMENT: Section 2.5, epidemiology studies: There is also Werner et al (2015) in pregnant women showing no association with maternal blood pressure. Environ Health. 2015 Sep 17;14: 75

RESPONSE: *Werner et al. (2015) was added to Table 2-5 and text in Section 2.5 (Cardiovascular, Epidemiology Studies; see below.*

In the pregnancy cohort, no associations were observed between maternal blood pressure or pregnancy-induced hypertensive disorders and DEHP metabolite concentration in maternal urine (Werner et al. 2015).

COMMENT: Section 2.9, Hepatic, Summary [re: "Human data on hepatic effects of DEHP are extremely limited, but suggest that occupational exposure levels may be associated with increased serum liver enzyme levels and decreased plasma cholinesterase activity"]: Perhaps say something about no literature on environmental exposures in relation to these outcomes.

RESPONSE: *A statement was added to Section 2.9, Summary indicating findings regarding these effects in the general population.*

> In cross-sectional studies of general population exposures, urinary metabolite levels were generally not associated with changes in triglyceride or cholesterol levels; there were no studies of other hepatic endpoints in humans exposed to DEHP in the environment or in consumer products.

COMMENT: Section 2.10, Renal, Epidemiology Studies [re: "In a study of Chinese workers exposed to DEHP at three different PVC manufacturing facilities . . . "]: Sample size?

RESPONSE: *Sample size information was added to the text:*

> In a study of 352 Chinese workers exposed to DEHP at three different PVC manufacturing facilities (average exposures ranging between 233 and 707 µg/m3 DEHP in the three factories), serum urea and creatinine levels did not differ from those in 104 unexposed workers (Wang et al. 2015).

COMMENT: Section 2.10, Renal, Epidemiology Studies [re: increased ACR]: Which indicates what? What is the meaning of that ratio?

RESPONSE: *Information was added to the text for clarity.*

> Elevated ACR indicates elevated protein levels in the urine and is a biomarker for kidney disease.

COMMENT: Section 2.13, Endocrine, Epidemiology Studies (Pancreas): Also James-Todd et al (2016) in pregnant women Environ Int. 2016 Nov;96: 118-126. doi: 10.1016/j.envint.2016.09.009. Epub 2016 Sep 17.

RESPONSE: *James-Todd et al (2016) was designated James-Todd et al. (2016a) and added to Tables 2-4 (maternal body weight) and 2-17 (maternal glucose homeostasis). Text for the study was added in Section 2.18 (Other Noncancer) and the acute oral MRL section as shown below. (Note: All glucose homeostasis studies were moved from Table 2-7 in Section 2.13 (Endocrine) to Table 2-17 in Section 2.18 (Other Noncancer).*

> Section 2.18 (Epidemiology Studies): A third cohort study reported reduced odds of having impaired glucose tolerance during pregnancy with increased DEHP concentration in maternal urine (James-Todd et al. 2016a).
>
> Acute Oral MRL: Available epidemiological studies suggest a potential ~~link~~ association between impaired glucose homeostasis and DEHP exposure, with reported associations between increased fasting serum glucose or insulin resistance and higher levels of DEHP metabolites in urine in some studies (James-Todd et al. 2016a…)… "

COMMENT: Section 2.13, Endocrine, Epidemiology Studies (Pancreas): Is there a biologic rationale for why impaired glucose homeostasis would also alter DEHP metabolism?

RESPONSE: *The statement was intended to convey that individuals with impaired glucose homeostasis may have increased urinary metabolites due to increased exposure due to disease state, not altered DEHP metabolism. The text was moved to Section 2.18 and revised to clarify the statement regarding reverse causation.*

> Section 2.18: ~~In addition,~~Finally, cross-sectional studies may also be vulnerable to spurious findings due to reverse causality~~,~~ if higher urinary metabolite levels ~~metabolism of DEHP is~~occur as a consequence of~~altered in persons with impaired glucose homeostasis~~ higher exposure via medications or personal care products in persons with impaired glucose homeostasis.~~)such that higher urinary metabolite levels occur.~~

COMMENT: Section 2.13, Endocrine, Epidemiology Studies [re: "In two cohort studies, no association…gestational diabetes was observed (Table 2-7)"]: See the James-Todd paper mentioned in the comment above

RESPONSE: *As indicated above, James-Todd et al (2016) was designated James-Todd et al. (2016a) and added to Table 2-17 (Note: Glucose homeostasis studies in adults were moved from Table 2-7 to Table 2-17). Text for the study was added in Section 2.18 (Other Noncancer) and the acute oral MRL section as shown below.*

> Section 2.18 (Epidemiology Studies): A third cohort study reported reduced odds of having impaired glucose tolerance during pregnancy with increased DEHP concentration in maternal urine (James-Todd et al. 2016a).

COMMENT: Section 2.13. Endocrine, Animal studies (Pancreas) [re: Several studies have . . . prenantal and/or early postnatal exposure studies]: Developmental

RESPONSE: *The paragraph has been moved to Section 2.17 (Developmental). There is a brief mention of these exposures in Section 2.18 (Other Noncancer) with a referring statement, as indicated below, added to the section.*

> Several developmental studies have also reported altered glucose homeostasis and impaired pancreatic β-cell function in rats following prenatal and/or early postnatal exposure to oral doses of 1–10 mg/kg/day (Lin et al. 2011; Mangala Priya et al. 2014; Rajesh and Balsubramanian 2014a)…See Section 2.17 (Developmental) for more details on these studies.

COMMENT: Section 2.13, Endocrine, Epidemiology Studies (Thyroid): There are several more recent studies:
Huang et al Sci Total Environ. 2018 Apr 1;619-620: 1058-1065. Yao et al Chemosphere. 2016 Aug;157: 42-8. doi: 10.1016/j

RESPONSE: *Huang et al. (2018) and Yao et al. (2016) were added to Table 2-7 and the text below added to Section 2.13.*

> In the largest of these (n=2,521 women; Yao et al. 2016), increased MEHP and MEHHP levels in first trimester urine were associated with decreased free and total T4 and increased TSH levels in maternal serum; no association was observed between total T3 levels and MEHP or MEHPP levels, and MEOHP levels were not associated with any thyroid hormone levels.

In a follow-up study of a different group of 98 Taiwanese women undergoing amniocentesis, increased MEOHP levels in the urine were associated with decreased TSH levels and increased MECPP levels were associated with decreased total T3 levels when data were combined across three time-points (one per trimester); none of the metabolites were associated with free or total T4 levels (Huang et al. 2018).

In two studies, no associations were observed between maternal urinary DEHP metabolite levels and cord serum thyroid hormone levels (Huang et al 2018; Yao et al. 2015).

COMMENT: Section 2.15, Neurological, Summary [re: " Human epidemiological data regarding neurological…limited. Based on available animal data, …not a sensitive target of DEHP neurotoxicity."]: I would argue that the animal literature (as reviewed here) appears quite limited as well and reflects mostly fairly crude measures (e.g. brain weight). I suspect that there are newer and more nuanced ways to assess neurological function that are now being used in the toxicological literature.

RESPONSE: *Animal studies include more refined measures that evaluated central and peripheral nervous system histology and brain weight. A limited number of studies evaluated neurobehavior (Dalgaard et al. 2000; Moser 1995, 2003). While additional testing could be done to improve the comprehensiveness of neurological evaluation, the adult neurological system does not appear to be a sensitive target of DEHP neurotoxicity based on available data.*

COMMENT: Section 2.16, Reproductive, Overview [re: "For studies that exposed animals both prior to and after sexual maturation (e.g., multigenerational studies) . . ."]: Also "two hit" studies

RESPONSE: *While "two hit" studies would fall into this category, no studies identified for DEHP were specifically designed to evaluate "two hit" exposures (one exposure prior to development, one exposure after development). Therefore, text was not edited to include this terminology to avoid confusion. The overview statement was revised to further clarify that this statement is referring to studies that span development and adulthood.*

Section 2.16: For studies that exposed animals both prior to and ~~after~~ through sexual maturation into adulthood (e.g., multigenerational studies) . . .

COMMENT: Section 2.16, Reproductive, Epidemiology Studies (Male Reproductive) [re: "Because serum testosterone levels vary over the course of the day, the lack of data on timing of sample collection (or consideration of timing in the statistical analysis) is an important limitation of these two studies"]: Very important point

RESPONSE: *No response necessary.*

COMMENT: Section 2.16, Reproductive, Epidemiology Studies (Male Reproductive) [re: "The remaining negative…appear well-conducted."]: Why is Mendiola et al 2012 being considered null? It suggests DEHP metabolites are associated with a number of changes in sex steroid hormones in men. Also Mendiola et al (2011) did not show an association between DEHP metabolites and T after adjusting for covariates, however there was an association with free androgen index and SHBG both of which capture other aspects of male sex steroid activity. As a more general point, T is not the only reproductive hormone in men so focusing on those results gives only one piece of the reproductive endocrine profile.

Similarly Meeker and Ferguson 2014 did observe associations in boys and to a lesser extent in older men, so calling it a negative study seems a bit of an overstatement.

RESPONSE: *To address the other reproductive hormones, data for free testosterone, estradiol, SHBG, LH, FSH, inhibin-B, and INSL-3 were added to Table 2-9. Data from the 12–20-year (peri- and post-pubertal) age group in Meeker and Ferguson (2014) were added to Table 2-9. The paragraph on testosterone levels was revised to reflect the association with free testosterone reported by Mendiola et al. (2102). New text that discusses associations with estradiol, SHBG, and INSL-3 was added to Section 2.16.*

> Section 2.16 (Epidemiology Studies, Male Reproductive Effects): Cross-sectional studies examining serum testosterone levels in men have ~~consistently~~ indicated associations between decreasing total and/or free testosterone levels and increasing urinary MEHP levels (Chang et al. 2015; Joensen et al. 2012; Jurewicz et al. 2013; Meeker et al. 2009a; Mendiola et al. 2012; Pan et al. 2006; Wang et al. 2016)…Among studies that did not observe any association with serum testosterone (Axelsson et al. 2015; Fong et al. 2015; Jönsson et al. 2005; Meeker ~~et al~~and Ferguson. 2014; Mendiola et al. 2011, 2012; Pan et al. 2015), two (i.e., Fong et al. 2015; Jönsson et al. 2005) did not report the timing of blood sample collection and did not consider time of sample collection in statistical analysis.
>
> Associations between urinary DEHP metabolites and other reproductive hormone levels in serum were also observed in males in several of these cross-sectional studies. Reduced serum estradiol was associated with increased urinary MEHP in four studies (Meeker et al. 2009a; Mendiola et al. 2012; Pan et al. 2015; Wang et al. 2016), and increased sex hormone-binding globulin (SHBG) was associated with increased urinary levels of MEHP (Mendiola et al. 2011), MEOHP (Chang et al. 2015; Mendiola et al. 2012), and MEHHP (Mendiola et al. 2012). None of the studies observed a relationship with luteinizing hormone (LH) or inhibin B, and 11 of the 12 studies that evaluated serum FSH observed no association with DEHP metabolites in urine.
>
> Only two of the cross-sectional studies examined serum levels of insulin-like factor 3 (INSL-3), a marker of Leydig cell function. Pan et al. (2015) observed an inverse association between INSL-3 and urinary MEHP, while Chang et al. (2015) saw no relationship with any DEHP metabolite.

A brief paragraph on the association between DEHP and serum T in prepubertal boys (6–12 years of age) from Meeker and Ferguson (2014) was added to Section 2.17, as effects in this age group are considered to be developmental.

> Section 2.17 (Developmental, Epidemiology Studies—Male Reproductive Development): In a cross-sectional study using NHANES (2011–2012) data, Meeker and Ferguson (2014) observed decreased serum testosterone associated with increased urinary levels of DEHP in a group of 134 boys ages 6–12 years (percent change -29.3; 95% CI -46.8, -6.10 for ∑DEHP). No other data on serum testosterone in prepubertal boys were located.

COMMENT: Section 2.16, Reproductive, Epidemiology Studies (Male Reproductive) [re: "However, none of these studies observed relationships"]: Not sure what this means given that you just described several relationships.

RESPONSE: *The studies in question do not show statistically significant associations, but taken together, they suggest a potential association. The sentence was deleted and preceding text revised as shown below.*

Most of the studies evaluating sperm morphology ~~indicated that~~ suggested potential weak associations between exposure to DEHP ~~was associated: with~~ and increased odds of sperm morphology below the World Health Organization (WHO) reference value for normal morphology (Han et al. 2014; Herr et al. 2009; Wirth et al. 2008) or a lower percent normal sperm with increasing DEHP exposure (Axelsson et al. 2015; Bloom et al. 2015a, 2015b; Huang et al. 2014b). ~~However, none of the studies observed relationships.~~

COMMENT: Section 2.16, Reproductive, Rodent Studies (Male Reproductive) [re: In Long-Evans rats…luteinizing hormone (LH) and testosterone…"]: This goes back to my earlier point about discussing hormones other than testosterone in the human literature. Why is LH included here but not in that section?

RESPONSE: *Data for other male hormones were added to Table 2-9. Associated text was revised as indicated in the previous response.*

COMMENT: Section 2.16, Reproductive, Nonrodent Mammalian Species (Male Reproductive) [re: "12-18 months old marmoset or 2-year-old Cynomolgus monkey]": Is this considered adult?

RESPONSE: *Sexual maturation in a marmoset monkey begins around 11–13 months, with complete sexual maturation around 18–20 months (Tardif et al. 2003, Comparative Medicine 53(4):364-368; Abbot and Hearn 1978, J Reprod Fert 53:155-166). Therefore, marmosets aged 12–18 months are considered peri- to post-pubescent. Therefore, the study exposing marmosets in this age group for 14 days (ICI Americas Inc 1982; Rhodes et al. 1986) was not considered developmental. Additionally, the study design was to compare effects between monkeys and adult rats, supporting that the study authors did not intend to evaluate developmental effects. However, the 65-week study in marmoset monkeys by Tomonari et al. (2006) was reclassified as developmental, as monkeys were exposed from weaning at 3 months through puberty at 18 months. The primary focus of this study was evaluation of landmarks of sexual development. The profile was revised to classify this study as a developmental study throughout Chapter 2 by indicating that the study exposed monkeys from weaning through sexual maturity. The LSE table and figure were updated accordingly. In the only other marmoset study, the age of monkeys exposed for 13 weeks was not reported (Kurata et al. 1998). Based on lack of discussion of development by study authors, it was assumed that monkeys were post-pubescent. Final body weights were greater than those reported for 18-month-old monkeys in the study by Tomonari et al. (2006).*

For Cynomolgus monkeys, the reported age range of male sexual maturity in Cynomolgus monkey is 3 years 8 months to 6 years (Smedley et al. 2002, Contemporary Topics 41(5):18-20). Therefore, the study in 2-year-old Cynomolgus monkeys by Pugh et al. (2000) should be considered a developmental study. The profile was revised to classify this study as a developmental study throughout Chapter 2 by indicating that the study was performed in sexually immature monkeys. The LSE table and figure were updated accordingly.

COMMENT: Section 2.16, Reproductive, Epidemiology Studies (Female Reproductive) [re: …DEHP exposure and prolonged time to pregnancy]: Also see Thomsen et al (2017) Hum Reprod. 2017 Jan;32(1): 232-238.

RESPONSE: *Data from Thomsen et al. (2017) were added to Table 2-11. Text in Section 2.16 (Reproductive) was revised as follows:*

> Three ~~two~~ prospective cohort studies of couples discontinuing birth control to become pregnant did not observe associations between DEHP exposure and prolonged time to pregnancy (Buck Louis et al. 2014; Jukic et al. 2016; Thomsen et al. 2017; Table 2-11).

COMMENT: Section 2.16, Reproductive, Epidemiology Studies (Female Reproductive): What does [lack of corroborating data] mean, that there have been no other studies on this topic to date? If so, perhaps rephrse to clarify.

RESPONSE: *The statement was revised (see below) to clarify that findings are inconclusive, in part, due to lack of evidence of decreased fertility in prospective cohort studies.*

> Multiple urine samples were collected for some of the women in this study, improving exposure estimates; however, the small population ~~study~~ size and lack of ~~corroborating data~~ evidence for decreased fertility in prospective cohort studies make the findings inconclusive.

COMMENT: Section 2.16, Reproductive, Epidemiology Studies (Female Reproductive) [re: Sathyanarayana et al. 2014]: We have updated this work in our newer, larger cohort: Sathyanarayana et al J Clin Endocrinol Metab. 2017 Jun 1;102(6): 1870-1878.

RESPONSE: *Data from Sathyanarayana et al. (2017) were added to Table 2-11. Section 2.16 (Reproductive) was revised as follows:*

> Four cross-sectional studies ~~Data~~ evaluating whether DEHP exposure alters reproductive hormones in women are limited and reported inconsistent findings (Table 2-11). A cross-sectional study in 591 pregnant women reported increased serum estrone and estradiol with increased MEHP and MEOHP urinary levels; no associations were observed with the sum of DEHP metabolites (Sathyanarayana et al. 2017).
>
> Reduced free testosterone in pregnant women was associated with higher urinary MECPP levels, but not levels of other DEHP metabolites, and no associations were observed between DEHP metabolites and total testosterone (Sathyanarayana et al. 2017).

COMMENT: Section 2.16, Reproductive, Epidemiology Studies (Female Reproductive) [re: Table 2-12]: There is also a small literature on menstrual cycling, most notably Jukic et al (2016) Environ Health Perspect. 2016 Mar;124(3): 321-8.

RESPONSE: *Details (see below) regarding menstrual cycling from Jukic et al. (2016) were added to the text in Section 2.16. These data were already included in the Female Reproductive Effect table (now Table 2-11 in the profile).*

> One of these studies (Jukic et al. 2016) evaluated the menstrual cycle, observing that DEHP metabolites were not associated with altered follicular phase length.

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Pregnancy Outcomes) [re: varying timing of recruitment or urine sample collection]: This is a very important point throughout the pregnancy studies and perhaps one that needs to be highlighted in the overview. The timing of urine sample collection is likely to have a very large impact on whether associations (if they exist) can be detected.

RESPONSE: *New text (below) was added to the Epidemiology Studies—Pregnancy Outcomes subsection (in Section 2.16) to highlight this point.*

> Importantly, the timing of urine sample collection may have a significant impact on a study's ability to detect an association. A systematic review of 15 studies recommends collection of samples in each trimester, standardization of sample collection to a specific time of day, and correction for specific gravity (not creatinine) to reduce intra- and within-individual variability (Yaghjyan et al. 2016).

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Pregnancy Outcomes) [re: preterm birth studies]: You might add that this suggests that particular pathways (e.g. inflammatory) may be particularly relevant.

RESPONSE: *A brief discussion of potential role of DEHP-induced inflammation was added (see below).*

> Ferguson et al. (2014a) proposed that increased risk of preterm birth may be associated with pro-inflammatory activities of DEHP based on positive associations between DEHP exposure and systemic markers of inflammation and oxidative stress (Ferguson et al. 2012). In support of this proposed mechanism, follow-up studies in this birth cohort showed a positive association between maternal urinary levels of DEHP metabolites and urinary levels of the oxidative stress marker, 8-isoprostane (Ferguson et al. 2015). Additionally, the association between urinary DEHP metabolites and spontaneous preterm birth was mediated by maternal urinary levels of 8-isoprostane using complex regression models (Ferguson et al. 2017).

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Pregnancy Outcomes) [re: pregnancy loss studies]: Also see: Messeerlian et al (2016) Epidemiology. 2016 Nov;27(6): 879-88

RESPONSE: *Data from Messerlian et al. (2016) were added to Table 2-12 as Messerlian et al. (2016b) and relevant information was added to the Epidemiology Studies—Pregnancy Outcomes subsection in Section 2.16; see below.*

> Pregnancy loss, or spontaneous abortion, was evaluated in three ~~two~~ cohort studies and one case-control study that measured exposure using urinary metabolites of DEHP. ~~The two cohort studies that examined early pregnancy loss reported contradictory findings: Jukic et al. (2016) observed a decrease in the odds of early pregnancy loss with higher exposure to DEHP, while Toft et al. (2012) reported an increase.~~ When evaluating early (or biochemical) pregnancy loss, one study observed decreased odds with increased urinary metabolite levels (Jukic et al. 2016), while two others reported increased risk of early pregnancy loss with an increase in urinary levels of one or more DEHP metabolites (Messerlian et al. 2016b; Toft et al. 2012). However, none of the three studies evaluating clinical pregnancy loss observed an association with exposure to DEHP (Messerlian et al. 2016b; Mu et al. 2015; Toft et al. 2012).

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Birth Size and Growth): Also Sathyanarayana et al 2016 Int J Environ Res Public Health. 2016 Sep 23;13(10)

RESPONSE: *Data from Sathyanarayana et al. (2016) were added to Table 2-13 as Sathyanarayana et al. (2016a). Section 2.17 was revised as below.*

> Only two ~~one~~ of the seven selected studies that examined infant length, weight, or head circumference ~~(Casas et al. 2016; Kim et al. 2016a; Shoaff et al. 2016; Su et al. 2014; Wolff et al. 2008; Zhao et al. 2014; see Table 2-14)~~ observed an association with DEHP metabolites in maternal or newborn urine (Sathyanarayana et al. 2016a; Zhao et al. 2014). …In contrast,

Sathyanarayana et al. (2016a) reported increased birth weight in female infants, but not male infants, with increasing DEHP metabolite levels in maternal urine.

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Birth Size and Growth)[re: However, birth weight…rendering the growth estimates uncertain]: Given this, I am not sure it's worth including this study.

RESPONSE: *The study was included because it met the defined inclusion criteria for human studies described in Appendix B. However, the limitations are clearly stated for the reader.*

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Male Reproductive Development) [re: AGD]: I am not sure you have said what AGD is yet.

RESPONSE: *AGD was defined in Section 1.2 of the profile (first use of abbreviation).*

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Male Reproductive Development): Also see: Sathyanarayana et al Environ Res. 2016 Nov;151: 777-782.

RESPONSE: *Data from Sathyanarayana et al. (2016) were added to Table 2-16 as Sathyanarayana et al. (2016b). Section 2.17 was revised as below.*

Sathyanarayana et al. (2016b) also did not find an increased risk of hypospadias and cryptorchidism and first trimester maternal urinary DEHP metabolites in male infants from a large birth cohort from four medical centers. However, increased maternal urinary DEHP levels were associated with an increased risk of hydrocele or all male genital anomalies combined.

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Male Reproductive Development) [re: Associations …decreased AGD and DEHP…reported in three…]: See also: Swan et al (2015) Hum Reprod. 2015 Apr;30(4): 963-72; Wenzel et al (2018) Environ Int. 2018 Jan;110: 61-70.

RESPONSE: *Citations for Swan et al. (2015) and Wenzel et al. (2018) were added to the text as seen below*.

Section 2.17 (male reproductive development): Associations between decreased AGD and DEHP metabolite levels in maternal urine ~~were~~ have been reported in ~~three~~ four birth cohorts (Barrett et al. 2016; Martino-Andrade et al. 2016; Suzuki et al. 2012; Swan 2008; Swan et al. 2015; Wenzel et al. 2018) ~~of the six cohorts~~.

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Male Reproductive Development) [re: Bustamante-Montes et al. (2013)…reduced penile length…maternal MEHP…no…corroborate finding]: The Martino-Andrade paper shows associations between 2nd trimester DEHP metabolites and newborn AGD

RESPONSE: *Martino-Andrade et al. (2016) was added to Table 2-16 in the row with the TIDES cohort (Barrett et al. 2016; Swan et al. 2015; Adibi et al. 2015). It was also added to the string reference for this cohort in Section 2.17 (see below).*

Section 2.17 (male reproductive development): Associations between decreased AGD and DEHP metabolite levels in maternal urine ~~were~~ have been reported in ~~three~~ four birth cohorts (Barrett et

al. 2016; Martino-Andrade et al. 2016; Suzuki et al. 2012; Swan 2008; Swan et al. 2015; Wenzel et al. 2018) ~~of the six cohorts~~.

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Female Reproductive Development) [re: Anofourchette distance…positive association… anoclitoral distance …change]: I would say that overall the results suggest no association for anofourchette distance either.

RESPONSE: *Revisions were made as follows:*

Section 2.17 (Female Reproductive Development): AGD in female infants has been assessed in ~~one~~ two pregnancy cohorts (Adibi et al. 2015; Barrett et al. 2016; Swan et al. 2015; Wenzel et al. 2018). No clear associations between maternal urinary DEHP metabolites and female infant anoclitoral or anofourchette distance were observed in either study (Table 2-16). ~~study (Adibi et al. 2015; Barrett et al. 2016; Swan et al. 2015); in this study, first trimester maternal urinary metabolite levels regression coefficients were -0.44–0.33 per natural log increase of the metabolites for anoclitoral or anofourchette distance measured at birth. Anofourchette distance indicated a positive association, whereas anoclitoral distance was not consistent in the direction of change.~~

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Female Reproductive Development) [re: The use of a single urine sample to estimate exposure is a significant limitation in these studies]: This is really a more general point that applies to the majority of human studies.

RESPONSE: *Text, as seen below, was added to Health Effects Section 2.1 (Introduction) to address the comment.*

Section 2.1: There are important limitations in the human epidemiological literature for DEHP. In particular, many of the epidemiological studies used a single spot urine sample to assess DEHP exposure. DEHP is rapidly metabolized and excreted, and urinary metabolite levels vary over time within an individual. Thus, a single urine sample may not correlate with long-term exposure patterns unless exposure levels remain very consistent. It is worth noting, however, that exposure to DEHP was probably relatively consistent for many years due to its ubiquitous presence in foods, packaging, and personal care products, until recent efforts to reduce or ban its use were initiated.

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Neurodevelopment) [re: "Most studies….Tellez-Rojo et al. (2103) and Huang et al. (2105) studies…repeated test scores…cumulative effects]: I'm not sure how 2 IQ tests would get at cumulative effects.

RESPONSE: *The sentence was revised to as shown below.*

Most studies administered the tests at one point in time, although Tellez-Rojo et al. (2013) and Huang et al. (2015) conducted longitudinal analyses, using repeated test scores in the same children ~~to assess cumulative effects.~~

COMMENT: Section 2.17 Developmental, Epidemiology Studies (Neurodevelopment) [re: "Other studies…psychomotor development…DEHP…"]: See also Doherty et al 2017: Environ Res. 2017 Jan;152: 51-58.

RESPONSE: *Doherty et al. (2017) was added to Table 2-15 and text in Section 2.17 was revised as seen below.*

> Other studies (Doherty et al. 2017; Factor-Litvak et al. 2014; Gascon et al. 2015b; Huang et al. 2015; Whyatt et al. 2012) did not observe associations between cognitive, mental, or psychomotor development and maternal urinary metabolites of DEHP (see Table 2-15).

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Neurodevelopment) [re: "However, the available studies measuring these endpoints…assess development…specific DEHP metabolites measured in urine"]: Not to mention differences across study populations as well

RESPONSE*: The sentence was revised to include study populations, as seen below.*

> However, the available studies measuring these endpoints are not strictly comparable, due to differences in the instruments used to assess development, varying ages at assessment, gestational timing of maternal urine collection, nature and number of covariates considered in the analyses, differences in study populations, and specific DEHP metabolites measured in urine.

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Neurodevelopment) [re: "Studies examining…DEHP exposure and autism…autism-related behavior…during pregnancy."]: Perhaps make the point that most conventional pregnancy cohort studies are underpowered to examine autism as an outcome.

RESPONSE: *The following sentence was added:*

> Both studies were small (137 children in New York and 175 children in Ohio), limiting their power to detect an effect on autism-related behaviors.

COMMENT: Section 2.17, Developmental, Epidemiology Studies (Neurodevelopment) [re: "There are no other studies to corroborate these [play behavior] data."]: The HOME study did not observe associations between prenatal DEHP and sex typical play (using a different inventory): Percy et al 2016: Environ Health. 2016 Aug 16;15(1): 87

RESPONSE: *Percy et al. (2016) was added to Table 2-15 and Section 2.17 was revised as follows.*

> Two cohort studies evaluated potential associations between gender-related play in children and maternal urinary DEHP metabolite levels (Table 2-15)… ~~Regression coefficients for reduced masculine play were -3.29 for MEHHP (95% CI -6.14, -0.43), -2.94 for MEOHP (95% CI -5.78, -0.10), and -3.18 for the sum of DEHP metabolites (95% CI -6.26, -0.10).~~ In contrast, the U.S. Health Outcomes and Measures of the Environment (HOME) birth cohort did not observe associations between maternal urinary metabolite levels and scores on the Gender Identity Questionnaire (GIQ) and the Playmate and Play Style Preferences Structured Interview (PPSI) measures of gender-related play in 227 children (101 boys and 126 girls, 8 years old) (Percy et al. 2016). Results from these studies are difficult to compare, primarily due to use of different metrics and different age at analysis. ~~There are no other studies to corroborate these data.~~

COMMENT: Section 2.17, Developmental, Mechanisms of Neurodevelopmental Toxicity: Do you need a heading here [after mechanisms of neurodevelopmental toxicity] to transition the next section since it looks like you're no longer considering neurodevelopment? For all of the sections that follow, given that you focus on animal studies, does that mean there's no literature on humans? In previous sections that was stated explicitly.

RESPONSE: *The Overview of Section 2.17 explicitly states what types of developmental data are available for humans and animals. It states that data available in both humans and animals included "birth size and growth, and development of the reproductive and neurological systems" and that "additional endpoints available only in animals include development of the endocrine, hepatic, and renal systems." Each subheading specifies if section contains human, animal, or mechanistic data. The subheadings for Section 2.17 are consistent with subheadings in other sections of the profile.*

COMMENT: Section 3.1 Toxicokinetics [re: "fetal tissues"]: Human?

RESPONSE: *The overview statement was revised to include the text below.*

DEHP has been detected in placenta, amniotic fluid, fetal liver, and other fetal tissues in exposed rats.

COMMENT: Section 3.1.2, Distribution (Human) [re: "DEHP has been detected in human adipose tissues… Contamination…DEHP detected in these studies"]: Given this limitation, I am not sure this needs to be included.

RESPONSE: *The study is included to avoid reporting bias. The text was revised as indicated below.*

While DEHP has been detected in human adipose tissues collected at autopsy (Mes et al. 1974), ~~.~~ ~~C~~contamination from plastics used in the handling and storage of the tissues may have contributed to the levels of DEHP detected in this study ~~these studies~~.

COMMENT: Section 3.3.1, Biomarkers of Exposure [re: "Despite the limitations…Johns et al. 2016…single urine sample…1 or 2 years]: Can you explain their rationale for why a single urine sample is sufficient for this long period given the low ICCs cited above?

RESPONSE: *The rationale of Johns et al. (2016) has been included, as seen below.*

Section 3.3.1 (Paragraph 6): Despite the limitations, urinary concentrations of DEHP metabolites are currently considered the optimal biomarkers for exposure.~~, and~~ Johns et al. (2016) conducted sensitivity and specificity studies to evaluate the ability of a single sample to correctly classify categories (e.g., highest tertile versus lowest) of exposure. Based on the results of these studies, Johns et al. (2016) concluded ~~suggested~~ that a single urine sample ~~was a~~ provides a reasonable ~~representation~~ means of categorizing ~~of~~ an individual's exposure over several months or possibly up to 1 or 2 years.

COMMENT: Section 5.2.1, Production. [re: "Table 5-1…companies…DEHP in 2015…"]: This is not really information on companies as much as locations by state.

RESPONSE: *Table 5-1 shows the number of facilities that produce, process, or use DEHP, organized by state. The reference to Table 5-1 in the text was revised for clarity.*

Table 5-1 summarizes the number and location of ~~information on~~ U.S. ~~companies~~ facilities that reported the use and production of DEHP in 2015 (TRI15 2016).

COMMENT: Section 5.5.4, Other Media [re: "Table 5-6 summarizes the detections of DEHP in various foods and beverages."]: It would be worth reiterating here that food is the primary source of exposure, a point that can get lost when so many different sources of exposure are described in this section.

RESPONSE: *The text was revised as seen below for clarity.*

As discussed in Section 5.6, food is the primary source of DEHP exposure in the general population.

COMMENT: Section 5.5.4, Other Media [re: Monitoring data …available data are in excess of 10 years old …current conditions: Wormuth et al (2006) has slightly newer data on European exposures through food and it is likely to be applicable to the US population as well (as far as broad categories of foodstuffs, etc…). Wormuth et al (2006) Risk Anal. 2006 Jun;26(3): 803-24.

RESPONSE: *Wormuth et al. (2006) was added as indicated below.*

Combined data from Europe, North America, and Asia show that the foods with the highest DEHP concentrations were animal fats, spices, and nut/nut spreads (Wormuth et al. 2006).

COMMENT: Section 5.6, General Population Exposure [re: "However, urinary levels for all metabolites… regulations to reduce…may be effective."]: You allude to this point in Chapter 1 (I noted the spot), but it might be worth putting this more detailed information there as well.

RESPONSE: *The following text was added to Section 1.1 (Overview and U.S. Exposures) to address the comment.*

In support, the National Health and Nutrition Examination Survey (NHANES) data show an overall decrease in urinary levels for all DEHP metabolites by approximately 2-fold or greater between 1999 and 2014 for a broad mix of the general public (CDC 2018; CPSIA 2008).

COMMENT: Section 5.6, General Population Exposure [re: "Hines et al. (2009b) explored….Only 2% ....Serum and urine….Median concentrations….Using an exposure…concentration of metabolites."]: I am not sure this is worth reporting on given the small sample size and low detection rate.

RESPONSE: *The study was retained in the profile to avoid reporting bias; however, a statement regarding limitations of the study was added at the end of the paragraph (see below).*

This study is limited by the small sample size and low detection rate.

COMMENT: Section 5.6, General Population Exposure [re: "The National Institute for Occupational Safety and Health…340,000 workers…early 1980s (NOES 1990)."]: Are there any more recent estimates?

RESPONSE: *There are not any recent exposure estimates based on review of NOES and non-confidential information from the EPA Chemical Data Reporter.*

COMMENT: Section 5.6, General Population Exposure [re: "Mean end-shift…17.9-34.4 (nail-only salons)."]: Perhaps mention nail salons more specifically given that all of the other occupational exposures mentioned are really the plastic industry so this represents a different set of at risk workers.

RESPONSE: *Nail salon data are now presented in a separate sentence (see below).*

Mean end-shift concentrations in plastic industries in µg/g creatinine were 3.75–25.4 (phthalate manufacturing), 16.7–158 (PVC film), 10.2–34.6 (vehicle filters), 12.1–124 (PVC compounding), 5.41–36.2 (rubber hoses), 5.37–69.3 (rubber boots), and 12.1–54.6 (rubber gaskets). In nail salons, mean end-shift concentrations were~~, and~~ 17.9–34.4 µg/g creatinine ~~(nail-only salons)~~.

COMMENT: Section 5.6, General Population Exposure [re: "One study explored …DEHP…North Carolina…<50% of the samples…made. Of the total….(up to 0.4 µg/L)."]: Again, not sure the results of this study are worth reporting.

RESPONSE: *The study was retained in the profile to avoid reporting bias; however, a statement (as seen below) regarding limitations of the study was added at the end of the paragraph.*

As previously noted, this study is limited by small sample size and low detection rate.

COMMENT: Section 5.6, General Population Exposure [re: "They also noted … higher DEHP concentrations."]: While treatment was ongoing or after decannulation?

RESPONSE: *Karle et al. (1997) was not explicit in reporting but based on text and Figure 3 of the report, patients treated for longer periods (e.g., 8 days) did not have higher DEHP levels during treatment than those treated for shorter periods (e.g., 4 days). The following revisions were made:*

Patients treated for longer periods did not have higher DEHP concentrations during treatment. The study ~~These~~ authors also reported that DEHP concentrations were below the detection limit in all patients before and after decannulation. ~~They also noted that patients treated for longer periods did not have higher DEHP concentrations.~~

COMMENT: Section 6.1, Information on Health Effects (Figure 6-1): Do you want to specify that the papers discussed in chapter 2 are not totally comprehensive (thus this figure doesn't fully capture the existing literature but just approximates it).

RESPONSE: *Text was revised and added as follows:*

Section 6.1: As noted in Section 2.1, both human and animal data were prioritized due to the extensive number of human and animal studies. Therefore, Figure 6-1 may not be inclusive of the entire body of literature. The criteria for study prioritization are further discussed in Appendix B. The purpose of this figure is to illustrate the information concerning the health effects of DEHP.

Figure 6-1 (footnote): *Includes only studies discussed in Chapter 2; the number of studies include those finding no effect; most studies examined multiple endpoints.

COMMENT: Section 6.3, Ongoing Studies [re: Table 6.1, investigator Anna Marie Vetrano]: This is definitely out of date- the PI [Anna Marie Vetrano] is no longer in academia. It might be worth double checking which of these are current. There are some new NIEHS studies to be added to this list as well (e.g. PI: J. Adibi, Pitt).

RESPONSE: *The RePORTER search was updated for Draft 4, and Table 6-1 was updated accordingly with information available as of October 4, 2018. Consistent with current information in RePORTER, the study listing Anna Marie Vetrano as a PI was deleted from Table 6-1. From the original 10 studies listed*

in the previous draft, there are now 29 reported though Pitt and Adibi that are not listed in the RePORTER.

Comments provided by Reviewer #3

General Comments (Reviewer 3)

COMMENT: In reviewing this document I note the following limitations:

- I do not have the capacity to independently verify the literature search and therefore assume that the search was complete.
- I do not have the capacity to independently verify information tables. I am therefore proceeding on the assumption that they are correct.

RESPONSE: *No response is necessary.*

ATSDR Charge Questions and Response (Reviewer 3)

Chapter 1

QUESTION: Do you agree with those effects known to occur in humans as reported in the text? If not, provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

COMMENT: I agree. I do not have independent knowledge of additional references.

RESPONSE: *No response is necessary.*

QUESTION: Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

COMMENT: The effects on animals and humans for immune, reproductive, and neurological effects tend to be very timing-specific.

RESPONSE: *No response is necessary.*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain.

COMMENT: See answer to question 2 [preceding question]. Document does not describe exposure from medical use of phthalate-containing materials. Since instrumentation and catheterization inside body and in contact with mucosa and ECMO interfaces blood with a huge surface area of membrane, this is a significant omission.

RESPONSE: *Potential exposure from medical devices in Section 1.1, Overview and U.S. Exposures, beginning with "For all age groups, the highest exposures to DEHP result from medical procedures….into the blood (FDA 2001). Exposures of neonatal…Huber et al 1996). For example…procedures (FDA 2001)." It is also discussed in Section 5.6, General Population exposure as noted: "Children's exposure…Karle et al. (1997)…decannulation." and "Latini and Avery (1999)…Plonait et al. (1993)…transfusion…blood received by patients." Lastly, Section 5.7,*

Populations with Potentially High Exposures, begins with a paragraph on these exposures and contains Table 5-17 (FDA Estimates of DEHP Exposures Resulting from Medical Treatments).

QUESTION: Do you believe the derived intermediate inhalation MRL value is justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: No comment by the Reviewer.

RESPONSE: *No response is necessary.*

QUESTION: Do you believe the derived acute oral MRL value is justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: No comment by the Reviewer.

RESPONSE: *No response is necessary.*

QUESTION: Do you believe the derived intermediate oral MRL value is justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: No comment by the Reviewer.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree that the data do not support derivation of acute inhalation, chronic inhalation, and chronic oral MRLs?

COMMENT: No comment by the Reviewer.

RESPONSE: *No response is necessary.*

Chapter 2

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature for DEHP?

COMMENT: Yes, to my knowledge.

RESPONSE: *No response is necessary.*

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)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: Yes generally, to my knowledge, but several key studies are not adequately described. Please note exceptions having to do with Roth 1988, David 2000 (both) and the Korean ADHD studies.

RESPONSE: *Please see responses in the Annotated Comments section below regarding these studies. Reviewer comments include a comment for Roth (1988) on p. 89, line 19 of the toxicological profile; a comment about David et al. (2000a, 2000b) on p. 113, line 1 of the toxicological profile, and a comment about the Korean ADHD studies (e.g., Park et al. 2014) on p. 270, line 8 of the toxicological profile.*

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)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT: Yes, to my knowledge.

RESPONSE: *No response is necessary.*

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?

COMMENT: Yes, to my knowledge.

RESPONSE: *No response is necessary.*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of Di(2-ethylhexyl)phthalate? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: No

RESPONSE: *No response is necessary.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for DEHP isomers?

COMMENT: No.

RESPONSE: *No response is necessary.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: Yes, to my knowledge.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?

COMMENT: Yes, to my knowledge.

RESPONSE: *No response is necessary.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain.

COMMENT: This is never the case that all possible mechanisms of action can be addressed, so it is a technical "no".

RESPONSE: *No response is necessary.*

Peer review of Unpublished Studies

The updated DEHP profile includes seven unpublished studies.

1. CMA. 1984. Initial submission: A 21-day dose relationship study of di(2-ethylhexyl) phthalate in rats (project report) with cover sheets and letter dated 041492. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8ECP. EPA Document No. 88-920002026. OTS053622. ttps: //ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0536220. July 18, 2017.

COMMENT: The study was certified as following good laboratory practice and in my opinion was adequately designed. However, the endpoint (peroxisomal proliferation) is of questionable relevance to humans. One particular animal (p. 29 [of unpublished study]) had an anomalous result that is summarily dismissed as not treatment related. This is not grounded in the evidence. A single case represents 20% of the animals in that group and the animal in question had a bile duct abnormality in the context of a chemical with hepatic effects. Thus, the report should not be considered to be "negative" but interpreted in context with the other studies in the body of evidence. For example, it may represent the presence of an innate or acquired susceptibility state. It should not be so readily dismissed.

RESPONSE: *ATSDR agrees that peroxisomal proliferation is of questionable relevance to humans. This endpoint from this study (and others) is discussed in the profile in Section 2.9 (Animal Studies—Elevated Liver weight and Hypertrophy, Enzyme Induction, Peroxisomal Proliferation), which begins with the following statement: "These endpoints are associated with hepatomegaly in animals, and may reflect adaptation of the liver to xenobiotic exposure; therefore, they may not be relevant to human health."*

Regarding the hepatic finding of marked individual cell necrosis with a ductal cell reaction in one lobe of the liver in 1/5 males, this information was added to the profile. However, the finding in one low-dose animal, without findings at higher doses, is below the threshold of toxicological significance. Therefore, the findings from this animal were not used as a basis for the hepatic LOAEL. However, ATSDR agrees

that this study should not be considered "negative." A hepatic LOAEL of 105 mg/kg/day was selected based on reduced serum lipids, a male reproductive LOAEL of 2,101 mg/kg/day was selected based on decreased testicular weight and atrophy, and a body weight serious LOAEL of 1,892 mg/kg/day was selected based on 38–44% decrease in body weight (see row 65 in Table 2-2).

Section 2.9 (*Animal Studies—Histopathology and Morphology*): Another study in F344 rats reported marked individual cell necrosis with a ductal cell reaction in one lobe of the liver in 1/5 males following dietary exposure to 105 mg/kg/day for 21 days; however, these lesions were not observed in males exposed to higher doses (667–2,101 mg/kg/day) or females at doses up to 1,892 mg/kg/day (CMA 1984). Because this finding was limited to a single animal at a low dose only, it is likely a spontaneous effect.

2. Exxon Chemical Americas. 1990. An investigation of the effect of di-(2-ethylhexyl) phthalate on rat hepatic peroxisomes with cover letter. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA Document8691000007729. OTS0530399. TSCATS/414999.

COMMENT: The study was certified as following good laboratory practice and in my opinion was adequately designed. However, the endpoint (peroxisomal proliferation) is of questionable relevance to humans.

RESPONSE: *As noted above, ATSDR agrees that peroxisomal proliferation is of questionable relevance to humans.*

3. ICI Americas Inc. 1982. Bis(2-ethylhexyl)phthalate: A comparative subacute toxicity study in the rat and marmoset with cover letter dated 032283. Submitted to the U.S. Environmental Protection Agency under TSCA, Section 8DS. EPA878220040. OTS215194. TSCATS/020230.

COMMENT: The study was certified as following good laboratory practice and in my opinion was adequately designed. However, the endpoint (peroxisomal proliferation) is of questionable relevance to humans.

RESPONSE: *As noted above, ATSDR agrees that peroxisomal proliferation is of questionable relevance to humans.*

4. Myers BA. 1992a. A subchronic (4-week) dietary oral toxicity study of di(2-ethylhexyl)phthalate in B6C3F1 mice (final report) with attachments and cover letter dated 040392. Eastman Kodak Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA 86920000874. OTS 0535432. https: //ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0535432. October 14, 2016.

COMMENT: The study was certified as following good laboratory practice and in my opinion was adequately designed. However, the endpoints, acute lethality and (peroxisomal proliferation), are of questionable relevance to humans. This was described as a subchronic feeding study but it much closer to an acute lethality or range-finding study and the dosage level was implausible for extrapolations to humans. This study did not adequately account for competing causes of death.

RESPONSE: *As noted above, ATSDR agrees that peroxisomal proliferation is of questionable relevance to humans. The study is classified as an intermediate-duration feeding study because animals at the lower doses survived exposure for 28 days. ATSDR considers any study duration 15–364 days to be intermediate duration. While the upper range of doses was extremely high, the lowest doses met*

inclusion criteria for animal studies discussed in Appendix B. Despite lack of accounting for competing causes of death, observed lethal doses are consistent with other studies that report death in laboratory animals following acute or intermediate exposure to doses of 1,000–5,000 mg/kg/day (see Figure 1-2 in the toxicological profile).

5. Myers BA. 1992b. Subchronic (13-week) dietary oral toxicity study of di(2-ethylhexyl)phthalate in Fischer 344 rats (final report) w-attachments and letter dated 040392 (missing pages 304 to 386). Eastman Kodak Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA 86920000875. OTS 0535433. https: //ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0535433. October 14, 2016.

COMMENT: The study was certified as following good laboratory practice and in my opinion was adequately designed. However, the endpoints are of questionable relevance to humans. This was described as a subchronic feeding study but it much closer to a range-finding study and the dosage level was implausible for extrapolations to humans.

RESPONSE: *ATSDR agrees that peroxisomal proliferation is of questionable relevance to humans. The study is classified as an intermediate-duration feeding study because animals at the lower doses survived exposure for 28 days. As discussed above, ATSDR considers any study duration 15–364 days to be intermediate duration. While the upper range of doses was extremely high, the lowest doses met inclusion criteria for animal studies discussed in Appendix B.*

6. Pegg, DG. 1982. Disposition of di-2-ethylhexyl phthalate following inhalation and peroral exposure in rats. Washington, DC: General Motors Corp. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA86910000683. OTS0530339.

COMMENT: The first page of the report of this study was missing from the copy provided and therefore it could not be determined if the study was certified as following good laboratory practice. However, in my opinion it was adequately designed to meet the purpose of toxicokinetics and distribution in vivo. This reviewer considers this study to be important background information confirming assumptions regarding distribution of phthalate absorbed by the inhalation route (which bypasses the liver on first pass, unlike feeding experiments).

RESPONSE: *No response is necessary.*

7. Schilling K, Deckardt K, Gembardt C, et al. 2001. Support: Di-2-ethylhexyl phthalate -two-generation reproduction toxicity study in Wistar rats continuous dietary administration, with cover letter dated 04/2/2001. Eastman Chemical Co. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. EPA89010000147. OTS0574025-1.

COMMENT: The study was certified as following good laboratory practice and in my opinion was well designed. The endpoints are of relevance to humans. It presents behavioural outcomes (water maze). This reviewer considers it to be a valuable addition to the literature.

RESPONSE: *No response is necessary.*

Regarding all seven unpublished studies:

QUESTION: Did the study use an adequate number of animals and practice good animal care?

COMMENT: Generally, yes. See specific comments.

RESPONSE: *No response is necessary.*

QUESTION: Did the study account for competing causes of death?

COMMENT: No. See specific example above.

RESPONSE: *See response above to comment for Myers (1992a).*

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

COMMENT: Some studies were operating at the limit of power, with n = 5.

RESPONSE: *No response is necessary.*

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

COMMENT: None of these study had a fatal flaw but all require mention in report and need to be interpreted in context of more recent studies.

RESPONSE: *All seven reports are included in the profile. Consistent with all studies cited in the profile, the body of literature is considered as a whole prior to making overall weight-of-evidence conclusions or interpretations.*

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

COMMENT: Yes, except as noted.

RESPONSE: *See responses above to noted exceptions, including concerns regarding "negative" interpretation of CMA (1984), lethality findings of Myers (1992a, 1992b), and questionable relevance of peroxisomal proliferation in CMA (1984), Exxon Chemical Americas (1990), ICI Americas Inc. (1982), and Myers (1992a, 1992b).*

Chapter 3

Toxicokinetics

QUESTION: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

COMMENT: Yes

RESPONSE: *No response is necessary.*

QUESTION: Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

COMMENT: I am unaware of other models but I am not working in this field.

RESPONSE: *No response is necessary.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT: No. I think that a more detailed comparative analysis in 3.1.6 would enhance the chapter.

RESPONSE: *The section was expanded, as detailed below, to include additional relevant details regarding toxicokinetics and potential species differences.*

> The toxicokinetics of DEHP in humans are generally similar to those that have been observed in monkeys, rats, mice, hamsters, and guinea pigs. As discussed in Section 3.1.1, oral absorption data indicate absorption of 11–70% in humans and 30–78% in laboratory animals. No reliable data are available regarding distribution in humans. Metabolic pathways are similar between species (Figure 3-1), although species differences in relative abundance of metabolites and glucuronide conjugates have been reported. Extensive oxidative metabolism of MEHP was demonstrated to occur in rats compared to humans, and metabolites were primarily unconjugated in rat urine, whereas conjugation with glucuronide was extensive in humans (Albro et al. 1982a); see Section 3.1.3 for additional details. Species differences in DEHP hydrolase activities have been reported, with much lower in human and marmoset liver tissue compared with rodent liver tissue (Ito et al. 2005, 2014). In both humans and laboratory animals, elimination is primarily via excretion in urine and feces (Daniel and Bratt 1974; Koch et al. 2004, 2005a; Kurata et al. 2012a, 2012b). Elimination half-lives for DEHP and MEHP did not differ widely between ~~across~~ species (Table 3-5).

Children and Other Populations that are Unusually Susceptible

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Please provide any relevant references.

COMMENT: Not that I am aware of.

RESPONSE: *No response is necessary.*

QUESTION: Is there a discussion of populations at higher risk of susceptibility? Do you agree with the choice of populations? Please explain and provide any additional relevant references.

COMMENT: Yes but I think that vulnerability (together with biological susceptibility) of children is poorly described and inadequate discussion of medical exposures and conditions.

RESPONSE: *It is not clear what aspects of vulnerability and susceptibility of children the Reviewer feels are poorly described. Section 3.2 (Children and Other Populations that are Unusually Susceptible) have entire sections discussing age-related exposure and pharmacokinetic differences and susceptibility. As noted previously, exposure due to medical equipment is discussed in Section 1.1 (Overview and U.S. Exposures), Section 5.6 (General Population Exposure), and Section 5.7 (Populations with Potentially High Exposure).*

Biomarkers of Exposure and Effect

QUESTION: Are the biomarkers of exposure specific for the substance? Please explain.

COMMENT: Yes, because metabolites are known.

RESPONSE: *No response is necessary.*

QUESTION: Are the biomarkers of effect specific for the substance? Please explain.

COMMENT: No.

RESPONSE: *No response is necessary.*

Interactions with Other Chemicals

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? Please explain and provide any additional references.

COMMENT: Yes, for what is known. No, because effects unlikely to occur at levels that would be encountered at a hazardous waste site.

RESPONSE: *No response is necessary.*

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

COMMENT: Not applicable.

RESPONSE: *No response is necessary.*

Chapter 4

QUESTION: Are any of the values or information provided in the chemical and physical properties tables wrong or missing? Please explain and provide any additional references.

COMMENT: No comment by the Reviewer.

RESPONSE: *No response is necessary.*

QUESTION: Is information provided on the various forms of the substance? Please explain.

COMMENT: No comment by the Reviewer.

RESPONSE: *No response is necessary.*

Chapter 5

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.

COMMENT: No comment by the Reviewer.

RESPONSE: *No response is necessary.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT: No comment by the Reviewer.

RESPONSE: *No response is necessary.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT: No comment by the Reviewer.

RESPONSE: *No response is necessary.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the Substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT: No comment by the Reviewer.

RESPONSE: *No response is necessary.*

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? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT: No comment by the Reviewer.

RESPONSE: *No response is necessary.*

Chapter 6

GENERAL COMMENT: See critique above. It is clear that there should be more studies on the inhalation route to support airborne exposure risk assessment and some studies examining mucosal contact and use of medical devices. Risk assessment for medical exposures is not supported by the database but may be of overriding importance for this class of chemicals. These are clearly needs, not just gaps, but pertain to a particular vulnerable group of people (patients) who may not be within the mandate of ATSDR to address.

RESPONSE: *ATSDR assumes that the critique that is mentioned in the comment relates to medical device comments received in Chapter 1 and Children and Other Populations that are Unusually Susceptible (Section 3.2) as these would appear in previous pages (i.e., above) of the peer review document. The responses to those comments are located within those sections. As stated at the beginning of Appendix B "The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to DEHP." While potential exposure to DEHP via use of medical devices was discussed in Sections 5.6 and 5.7, identification of potential health hazards specifically associated with medical exposures is outside the scope of the profile. Pertaining to the need for inhalation studies mentioned in the comment, ATSDR agrees that more inhalation studies are needed to support inhalation MRLs. Section 6.2 (Identification of Data Needs) states that additional acute inhalation toxicity studies, low-exposure intermediate inhalation toxicity studies, and chronic inhalation toxicity studies are needed.*

QUESTION: Do you know of other studies that may fill a data gap? Please provide any relevant references.

COMMENT: No

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with the identified data needs? Please explain.

COMMENT: Yes

RESPONSE: *No response is necessary.*

QUESTION: Are the data needs presented in a neutral, non-judgemental fashion? Please note any bias in the text.

COMMENT: I do not think that the presentation is biased.

RESPONSE: *No response is necessary.*

Chapter 7

QUESTION: Are you aware of any additional regulations or guidelines that we should add? Please provide citations.

COMMENT: I am not aware of any.

RESPONSE: *No response is necessary.*

QUESTION: Are there any that should be removed? Please explain.

COMMENT: No.

RESPONSE: *No response is necessary.*

Appendix A – Minimal Risk Levels (MRLs)

Inhalation Acute MRL

QUESTION: Do you agree or disagree with the lack of an inhalation acute MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: Agree. This is not a priority for resolution because Intermediate MRL should be sufficiently protective.

RESPONSE: *No response is necessary.*

Inhalation Intermediate MRL

QUESTION: Do you agree or disagree with the proposed inhalation intermediate MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: I agree. Given the paucity of information and the need for extrapolation, this is the best that can be done, in my opinion, and is appropriately conservative.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose

COMMENT: Until we have more insight into species comparability on matters such as timing and stage of development, I think the 3 × 10 × 10 model is reasonable as a first approximation.

RESPONSE: *Thank you. As you indicated, uncertainty factors of 3 x 10 x 10 were used in deriving this MRL.*

Inhalation Chronic MRL

QUESTION: Do you agree or disagree with the lack of an inhalation chronic MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: Understand the reason it is absent, but this is a significant omission. For this chemical, chronic inhalation is an exposure scenario of considerable importance and concern, especially for occupational exposure. If and when new data become available this should be remedied.

RESPONSE: *ATSDR understands your concern. Currently, ATSDR does not have data that support derivation of a chronic-duration inhalation MRL. ATSDR reviews new data during future revisions of the DEHP profile. Occupational exposure health guidance values are addressed by the Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health.*

Oral Acute MRL

QUESTION: Do you agree or disagree with the proposed oral acute MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: Agree. Given the practical difficulties modeling a response and the influence on the exposure-response cure of highest (last) dose, using the take-off point by BMR estimation is about the only option.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: As above. I am comfortable with this ΣUF and its derivation.

RESPONSE: *No response is necessary.*

Oral Intermediate MRL

QUESTION: Do you agree or disagree with the proposed oral intermediate MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: I do not disagree, which probably should be counted as Agree but comes with caveats. It seems clear that the estimate of take-off point is close to the highest value, which is forcing the model and producing greater uncertainty. So I concur with provisional use unless and until there are data to

clarify the relationship (which may or may not be forthcoming). Part of the problem might be that immune, reproductive, and endocrine effects do not necessarily have linear exposure-response relationships because they depend on timing, random variables, age/maturation, and periodicity more than other pathophysiological responses. Better understanding of mechanism may help resolve these issues but for now the proposed oral intermediate MRL is more likely than not well within the bounds of precaution and this is unlikely to present a problem.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: No. See above.

RESPONSE: *No response is necessary.*

Oral Chronic MRL

QUESTION: Do you agree or disagree with the lack of an oral chronic MRL value? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: Agree. Understand the reason it is absent, but this is a significant omission. For this chemical, consumption is an exposure scenario situation of moderate concern. If and when new data become available this should be remedied.

RESPONSE: *ATSDR understands your concern. Currently, ATSDR does not have data that support derivation of a chronic-duration oral MRL. ATSDR reviews new data during future revisions of the DEHP profile.*

QUESTION: Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT: No comments.

RESPONSE: *No response is necessary.*

Appendix B – Literature Search Framework

QUESTION: Does Appendix B provide a sufficiently clear documentation of ATSDR's health effects literature search strategy and inclusion/exclusion criteria?

COMMENT: Does not indicate whether search was limited to English language. (All references are in English, which suggests possible omissions because in the 1980's it was common for scientific reports to appear in other languages and phthalates were of concern widely (esp. Germany.)

RESPONSE: *As stated in Section B.1, "ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions." The statement below was added to Appendix B (B.1 Literature Search and Screen) for clarification.*

> Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as IARC documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested.

QUESTION: Does it provide enough transparency regarding ATSDR's implementation of its inclusion and exclusion criteria (e.g., how ATSDR chose the studies it included in the health effects chapter)?

COMMENT: Yes. Description is inadequate on search and evaluation of gray literature.

RESPONSE: *Text was added (as detailed below) in Appendix B (B.1.1 Literature Search) to better describe search and evaluation of grey literature.*

> ATSDR also identified reports from the grey literature from searches described in Table B-3, ~~which included~~ including unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, theses, and dissertations. Relevant unpublished studies were submitted to three peer reviewers for evaluation of animal care, dose adequacy, number of animals in dose groups, study design and reporting, and whether the reviewer agreed with the author's conclusive statements. Unpublished studies of a questionable nature were not included in the toxicological profile.

Overall Usability of the Profile

QUESTION: Does the new chapter organization make it easier for you to find the information you need? For example, are you satisfied with the organization of the health effects chapter by organ system rather than exposure route?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Does the profile contain all of the information you need? If no, please elaborate on what additional information would be helpful.

COMMENT: For this Profile, see above. There is insufficient information on medical exposure to the chemical class. This may reflect mission of ATSDR but for this chemical it is significant.

RESPONSE: *As discussed above, medical exposures are discussed in Section 1.1, Section 5.6, and Section 5.7 (first paragraph). Risk assessment based on medical exposure is outside the scope of ATSDR toxicological profiles.*

QUESTION: If you have previously used any Toxicological Profile(s) for your work, which parts or content are the most useful to you, and what do you use it for?

COMMENT: I have used the Profiles often, most Chapters 2 and 3; also 4 is there are exposure questions or specific issues relevant to my work. Chapter 5 is very useful but I happen not to use it as

much as the others. I have never found MRLs particularly useful in my work and consider them administrative guidance in priority setting, not a useful benchmark in toxicology.

RESPONSE: *No response is necessary.*

QUESTION: Are the new tables and figures clear and useful? Do they make the toxicological profile easier to read?

COMMENT: No comment by the Reviewer.

RESPONSE: *No response is necessary*

Annotated Comments (Reviewer 3)

COMMENT: p. 1, lines 32, 33. Term "false positives" is not quite right. Suggest: "potentially leading to reports of the presence or elevation of phthalate concentrations due to contamination." The test for phthalate is not false in the presence of contamination; it is the source characterization.

RESPONSE: *Section 1.1, Overview and U.S. Exposure, the sentence was revised in a manner consistent with the Reviewer's suggestion (see below).*

> It is very difficult to determine these low levels accurately since DEHP is ubiquitously present in laboratory equipment, potentially leading to false identification of elevated phthalate concentrations due to sample contamination ~~reports of false positives~~ (Howard et al. 1985).

COMMENT: p. 2, line 2. Term "exudes" is incorrect, because this means to actively discharge some substance. Better terms would be "leach", elude", or "extract".

RESPONSE: *Section 1.1, Overview and U.S. Exposures, the text was revised as seen below.*

> In adults and children, ingestion of food (including food from containers that ~~exude~~ leach DEHP) accounts for approximately 95% of total oral exposure, with the remaining exposure attributed to dust ingestion (Clark et al. 2011).

COMMENT: p. 2, line 3. Incorrect statement: "Since toddlers and infants consume less food than older children and adults, ingestion of food and dust particles containing DEHP have approximately equal exposure significance." This is dead wrong. Toddlers and influence consume much more food (and water, much in formula) per unit body weight (and body surface area). That, and their vulnerability with respect to development, means that the exposure is much *more* important in young children. *This must be corrected.*

RESPONSE: *Section 1.1, Overview and U.S. Exposures: The following revisions were made:*

> ~~Since toddlers and infants consume less food than older children and adults, ingestion of food and dust particles containing DEHP have approximately equal exposure importance~~ In toddlers and infants, ingestion of food and dust particles containing DEHP have approximately equal contributions to total oral DEHP intake (Clark et al. 2011).

COMMENT: p. 2, line 5. "Occupational exposures may be significant, but the highest exposures …" What? This is a false comparison. Better: "Occupational exposures may be significant in some settings. For all age groups, the highest exposures occur in medical procedures …."

RESPONSE: *The text was revised as suggested (see below).*

Section 1.1, Overview and U.S. Exposures: Occupational exposures may be significant in some settings. ~~,~~For all age groups, ~~but~~ the highest exposures to DEHP result from medical procedures such as blood transfusions (upper bound limit of 8.5 mg/kg/day) or hemodialysis (upper bound limit of 0.36 mg/kg/day), during which DEHP may leach from plastic equipment directly into the blood (FDA 2001).

COMMENT: p. 3, line 8. "…cumulative risk assessment to" should be "cumulative risk assessment model to"

RESPONSE: *The text was revised as suggested (see below).*

Section 1.2, Summary of Health Effects: Due to their similarity of effects, the National Academy of Sciences (NAS) recommends applying a cumulative risk assessment model to phthalates as a chemical group rather than conducting separate assessments on individual phthalates (EPA 2012; NAS 2008).

COMMENT: p. 6, line 28. Phrasing "Data from oral rodent studies indicate the alteration of several organ systems other than the reproductive system…" is incorrect. Should be: "Data from oral rodent studies indicate the alteration of several organ systems in addition to the reproductive system…"

RESPONSE: *The text was revised as suggested (see below).*

Section 1.2, Summary of Health Effects, Developmental Effects: Data from oral rodent studies indicate the alteration of several organ systems ~~other than~~ in addition to the reproductive system with early life DEHP exposure.

COMMENT: p. 9, line 34. Last sentence should read "…phthalates from medical equipment and supplies, especially disposable plastic items."

RESPONSE: *The text was revised as suggested (see below).*

Section 1.2, Summary of Health Effects, Cancer Effects: Furthermore, cancer treatments could increase exposure to, and excretion of, phthalates from medical equipment and supplies, especially disposable plastic items.

COMMENT: p. 74, line 15. Omitted word: …evaluated **in** a review by…."

RESPONSE: *The omitted word "in" was added as seen below.*

Section 2.3, Body Weight (Overview): Potential mechanisms of obesity have been evaluated in a review by Kim and Park (2014).

COMMENT: p. 74, line 19. Suggest substituting "a" for "any" in line three of "Epidemiology Studies". "Any" is too strong and unnecessary.

RESPONSE: *The text was revised as suggested (see below).*

Section 2.3, Body Weight (Epidemiology Studies): The systematic review conducted by Goodman et al. (2014) concluded that the available data (through June, 2013) evaluating obesity outcomes and phthalate exposure did not indicate a~~ny~~ consistent association between DEHP and BMI, waist circumference, or fat distribution.

COMMENT: p. 86, line 2. First line: Substitute "covariation" for "correlations". Covariation means that factors change together for a reason, while correlation refers to the statistical trends being in parallel.

RESPONSE: *The text was revised as suggested (see below).*

Section 2.3 Body Weight, (Epidemiology Studies): The epidemiological data on DEHP metabolite levels and obesity parameters may be confounded by ~~correlations~~ covariation among body weight, caloric intake, dietary composition (e.g., processed versus unprocessed foods), urinary creatinine levels, and DEHP exposure.

COMMENT: p. 88, line 17. Change "…numerous limitations, including …." To "numerous limitations arising from". The limitations are the result of study design and lack of control for confounding.

RESPONSE: *The text was revised as suggested (see below).*

Section 2.3 Body Weight, (Summary): However, most of these studies have numerous limitations ~~, including~~ arising from cross-sectional design and lack of consistent control for potential confounders

COMMENT: p. 89, line 19 [re: Unusual lung effects…4 weeks after birth…preterm infants (Roth et al. 1988)]: Important in reviewing Roth 1988 to be sure that the children did not actually have hyaline membrane disease, as they were preterm. Appearance of a new-onset respiratory distress syndrome with same characteristics at four weeks is indeed unusual and further information must be provided. Were they on a ventilator for four weeks and was that the basis for their exposure? Was barotraumas ruled out? All of these factors are critical to plausibility of such a dramatic cite.

RESPONSE: *Additional information (see below) from the study was added to address the Reviewer's questions.*

Section 2.4, Respiratory (Epidemiology Studies): These infants initially showed improvements after birth prior to progressive alterations in the lungs, which were not attributable to typical lung damage associated with artificial ventilation (e.g., oxygen toxicity, barotrauma, or bronchopulmonary dysplasia).

COMMENT: p. 103, line 22. Spongiosis hepatis is an uncommon pathological outcome in rats and most readers are likely to be unfamiliar with it. Suggest a brief description/definition.

RESPONSE: *A brief description was added (see below).*

Section 2.9: In chronic studies in F344 rats, observed hepatic lesions other than hepatocellular hypertrophy included spongiosis hepatis (cystic degeneration)…"

COMMENT: pp. 106 – 107, line 33. "Findings for induction of peroxisomal catalase are mixed,…" This almost certainly is because of other factors mediating catalase expression, indicating that phthalate exposure is only one of several factors in phthalate-exposed animals. Either say so or clarify under what circumstances catalase activity was increased or reduced.

RESPONSE: *Text was added as seen below.*

Section 2.9, Hepatic (Animal Studies—Elevated Liver Weight and Hypertrophy, Enzyme Induction, Peroxisomal Proliferation): Findings did not show a clear pattern with respect to strain, sex, or exposure duration, and may be mediated by factors unrelated to DEHP exposure.

COMMENT: p. 107, line 29. "The mechanistic key events include: (1) PPAR activation," would be better stated "The key mechanistic events" and specification of which PPAR (most likely α).

RESPONSE: *The text was revised as seen below.*

Section 2.9, Hepatic (Mechanisms of Hepatic Toxicity): The key mechanistic ~~key~~ events include: (1) PPAR activation (most likely α); (2) peroxisome proliferation . . .

COMMENT: p. 108, line 2. PPARβ is European usage for what is usually called PPARδ in US. Please check for correct usage.

RESPONSE: *The text was revised (as seen below) to use the standard U.S. nomenclature of PPARδ.*

Section 2.9, Hepatic (Mechanisms of Hepatic Toxicity): MEHP activates mouse and human PPARα, PPAR~~β~~δ, and PPARγ.

COMMENT: p. 113, line 1. Unclear passage: "The relevance of the kidney effects observed in the dietary studies in rats and mice is unclear because some of the findings (David et al. 2000a, 2000b) indicate that they may reflect exacerbation of age-, species-, and/or sex-related lesions by DEHP and not accompanied by evidence of impaired kidney function." What is meant by this? As written, it implies that DEHP has an effect of amplifying or exaggerating normal changes by age, species, and by sex, with no functional effect. Please clarify. Also, correct term for a permanent shift in baseline is not exacerbation, but aggravation, at least as used in human functional capacity.

RESPONSE: *The Reviewer's interpretation of the remark is correct. The text was revised for clarity (see below). In terms of animal studies, exacerbation is an appropriate term to describe an increase in effects associated with age, species, and/or sex.*

Section 2.10, Renal (Animal Studies): The relevance of the kidney effects observed in the dietary studies in rats and mice is unclear. ~~because s~~ Some of the findings (David et al. 2000a, 2000b) ~~indicate that they may reflect~~ suggest exacerbation of typically observed age-, species-, and/or sex-related lesions following ~~by~~ DEHP exposure ~~and not accompanied by~~ in the absence ~~evidence~~ of impaired kidney function.

COMMENT: p. 115. Is glucose intolerance induced by DEHP a short-term or a long-term phenomenon? In other words, is there evidence that glucose levels go up acutely after DEHP exposure or is the evidence for a long term trend toward elevated glucose levels after chronic exposure? This is very important.

RESPONSE: *All human data are from cross-sectional studies, so it is not possible to tell if effects are acute or long-term. The glucose homeostasis discussion was moved from the endocrine section to Other Noncancer (Section 2.18). It is not possible to answer this Reviewer's question based on adult animal studies, as glucose levels were not monitored at multiple time points in available studies. However, evidence from developmental animal studies indicate the potential for long-term alterations in glucose*

homeostasis, as altered glucose homeostasis was observed in adult offspring following exposure to DEHP only during gestation and/or lactation (Lin et al. 2011; Mangala Priya et al. 2014; Rajesh and Balasubramanian 2014a). The following was added.

Section 2.18, Other Noncancer (Epidemiology Studies): Additionally, due to the cross-sectional design, it is not possible to determine if reported changes in glucose homeostasis in some studies are acute reactions to exposure or represent a trend toward increased blood glucose following chronic exposure to DEHP.

COMMENT: p. 124, line 7. "observe" should be "observed".

RESPONSE: *The typographical error was corrected as seen below.*

Section 2.13, Endocrine (Animal Studies—Adrenal Gland): These changes were not observed in PND 21 offspring.

COMMENT: p. 126, line 1. Unclear passage: "In isolated glomerulosa cells, DEHP increased the regulation of genes associated with the angiotensin II and potassium pathways". Is it meant that DEHP upregulated these genes and increased activity of synthesizing enzymes? It doesn't make sense that a factor would increase regulation of something that is already highly regulated.

RESPONSE: *The indicated passage was revised for clarity (see below).*

Section 2.13, Endocrine (Animal Studies—Adrenal gland): In isolated glomerulosa cells, DEHP increased many of the same ~~the regulation of~~ genes ~~associated with the~~ upregulated by angiotensin II and potassium ~~pathways~~, including genes encoding potassium channels, at PND 60~~,~~ but not PND 21 (Martinez Arguelles et al. 2013).

COMMENT: p. 136. [re: Ku et al. (2015) measured only MEHP and MEHHP…misclassification of DEHP exposure in these studies.]: Absence of data on other metabolites and other phthalates would not lead to misclassification if MEHHP is a valid surrogate (i.e. if its concentration tracked along with other phthalates and their metabolites and so could be used as an indicator for the chemical class. Do we have data on that? (See p. 179, bottom of page, for findings suggesting this is plausible.)

RESPONSE: *The text regarding misclassification was deleted and text was added as seen below.*

Section 2.14, Immunological (Epidemiology studies): ~~Ku et al. (2015) measured only MEHP and MEHHP, and Whyatt et al. (2014) measured only MEHHP; lack of data on the other metabolites may lead to misclassification of DEHP exposure in these studies.~~ No association was seen in the other studies, possibly due to bias or analysis limited to a subset of DEHP metabolites (Ku et al. 2015; Whyatt et al. 2014).

COMMENT: p. 150, line 26. "However, none of the studies observed relationships." Relationships were observed. Better to say: "However, none of the studies characterized relationships."

RESPONSE: *The studies in question suggest a potential association. The text preceding the sentence was revised and the sentence was deleted, as seen below.*

Section 2.16, Reproductive (Epidemiology Studies—Male Reproductive Effects): Most of the studies evaluating sperm morphology ~~indicated that~~ suggested potential weak associations between exposure to DEHP ~~was associated: with~~ and increased odds of sperm morphology below the World Health Organization (WHO) reference value for normal morphology (Han et

al. 2014; Herr et al. 2009; Wirth et al. 2008) or a lower percent normal sperm with increasing DEHP exposure (Axelsson et al. 2015; Bloom et al. 2015a, 2015b; Huang et al. 2014b). ~~However, none of the studies observed relationships~~

COMMENT: p. 210 – 211. Much is made of the "non-monotonic" changes in testosterone levels. The implication is that this is an inconsistency and there should be a predictable exposure-response relationship and that the absence makes its "biological relevance" "unclear". That expectation may not hold true for first-generation endocrine effects because of multiple feedback mechanisms in both dam and offspring. T is a hormone, not a chemical xenobiotic, and acts on a receptor and there are multiple opportunities for saturation effects, upregulation, and timing differences. Suggest "unclear, pending further study of the pituitary-testes axis". The reason that this is important is that testicular testosterone disruption is a significant effect, predicted to occur in humans, and the basis for risk assessment. The impression should not be left that this is either a failure to confirm that it occurs or of no consequence. It may be an important, multi-tiered complicated effect with adaptation and feedback. *The next paragraph gets it right,* by mentioning the axis and signaling to the reader the complexity of response.

***RESPONSE**: The text was revised as shown below.*

Section 2.17, Developmental (Animal Studies—Male Reproductive Development):
The significance of this non-monotonic response is unclear without further study of the pituitary-testes axis.

The biological relevance of the non-monotonic dose response relationship for fetal testosterone is also unclear without further study of the pituitary-testes axis.

COMMENT: p. 215, line 32. Double period.

***RESPONSE:** The extra period was deleted in the following sentence:*

Section 2.17, Developmental (Epidemiology Studies—Neurodevelopment): Many epidemiological studies assessed neurodevelopmental outcomes.

COMMENT: p. 228, line 22. Typo. "this studies" should be "this study".

***RESPONSE:** The grammatical error was corrected as shown below.*

Section 2.17, Developmental (Animal Studies—Pancreatic Development (Glucose/Insulin Homeostasis)): However, this stud~~ies~~y suggests that DEHP-induced changes in insulin tolerance may be mediated via PCNA.

COMMENT: p. 229, bottom. There is a logical inconsistency in declaring increased liver weight to be of uncertain relevance and using it to define a NOAEL but reporting other aspects of hepatic toxicity as candidate endpoints for toxicity. In the absence of a study showing that hepatic hypertrophy is benign, should it not be assumed that this effect is the first step in an exposure response relationship? Rationale!

***RESPONSE:** The rationale for considering effects associated with hepatomegaly is discussed in depth in Section 2.9, Hepatic (Animal Studies—Elevated Liver Weight and Hypertrophy, Peroxisomal Proliferation, Enzyme Induction), and is based on the conclusions of the expert panel convened by the European Society of Toxicology Pathology (summarized by Hall et al. 2012). Instead of repeating the*

complete rationale again, the reader is referred back to Section 2.9 (see below). Additionally, a short rationale was added and the NOAEL sentence was deleted.

Section 2.17, Developmental (Animal Studies- Liver System Development): As discussed in detail in Section 2.9 (Hepatic Effects), increased liver weight without histological evidence of hepatobiliary damage is not considered adverse or relevant for human risk assessment unless at least two of the following are observed: (1) 2–3 times increase in ALT levels; (2) biologically significant change in other biomarkers of hepatobiliary damage (ALP, AST, GGT, etc.); or (3) biologically significant change in another clinical pathology marker indicating liver dysfunction (Hall et al. 2012). Therefore, evidence of increased liver weight alone is not used as a basis for a LOAEL~~. Due to uncertain human relevance of these findings (Hall et al. 2012), they are considered NOAELs (see Section 2..9 for more details).~~

COMMENT: p. 231. The MFO system is thought to exist (teleologically) to degrade endogenous compounds as well as to protect the organism after intake of toxic organic agents in food. Thus a reduction in metabolism of artificial xenobiotics into more toxic metabolites may be more or less beneficial in a polluted environment but it hardly constitutes a biological benefit to the organism in terms of normal physiological function.

RESPONSE: *The following text was added and the sentence regarding MFO and benefit was deleted.*

The potential adversity of observed changes in the MFO enzymes on the liver is difficult to determine in the absence of evaluation of other hepatic endpoints. Changes could potentially lead to altered metabolism of endogenous and exogenous chemicals, resulting in decreased detoxification of chemical and/or decreased formation of toxic intermediates. ~~The effect of the changes in the MFO enzymes on the liver is difficult to evaluate. Although the MFO system tends to process various foreign chemicals and thus be of benefit, some of the oxidized metabolites produced by the initial MFO reactions are more toxic than the parent compound.~~

COMMENT: pp. 260 – 262. Fine discussion of toxicokinetics but fails to convey the magnitude of enterohepatic circulation. Is it a major mechanism of metabolite conservation or a minor or negligible part of re-absorption? What is the empirical evidence? P. 263 suggests differences based on species tissue characteristics, as well.

RESPONSE: *Based on the page numbers provided in the comment, ATSDR assumes that the Reviewer is referring to Section 3.1.5 (PBPK/PD Models). The available data on the magnitude of enterohepatic circulation and species differences is presented in Section 3.14, Excretion, the paragraph begins with "Estimates of the relative contribution..." and ends with a citation of Kurata et al. (2012b).*

COMMENT: p. 267, line 12. Suggest reminding readers what these lethal effects were, as it is hard to keep track.

RESPONSE: *The term lethal indicated death; the text was revised for clarity (see below).*

Section 3.2, Children and Other Populations that are Unusually Susceptible (Age-Related Differences in Susceptibility): For example, acute DEHP doses associated with lethality are lower in younger rats ~~have been shown to be more susceptible to the acute lethal effect of high doses of DEHP~~(Dostal et al. 1987; Tonk et al. 2012).

COMMENT: p. 270, line 8. This research must be explained more fully. Do you mean to say that in Korean children with ADHD there is evidence of binding of MEHP to the dopamine receptor (in a

peripheral receptor? In the CNS?) compared to controls and a correlation with performance testing over time? This must be clarified!

RESPONSE: *Text was revised (as seen below) to include a more detailed explanation of this study. The study did not evaluate receptor binding. It looked at polymorphisms at major candidate genes for attention-deficit/hyperactivity disorder (ADHD) with regards to neuropsychological performance in 179 Korean children with ADHD.*

Section 3.2, Children and Other Populations that are Unusually Susceptible (Genetic Polymorphisms Altering Susceptibility): Park et al. (2014) investigated potential genotype-phthalate interactions between urinary levels of phthalate metabolites (including MEHP and MEOHP) and polymorphisms at major candidate genes for attention-deficit/hyperactivity disorder (ADHD) with regard to neuropsychological performance in 179 Korean children with ADHD. An increase in DEHP urinary metabolites was associated with poor attentional performance in children with the dopamine receptor D4 (DRD4) gene 4/4 variant, but not in children without the DRD4 4/4 genotype. This suggests that the DRD4 4/4 genotype may increase susceptibility to the effects of DEHP. ~~observed significant interactions between urinary levels of DEHP metabolites (MEHP and MEOHP) and dopamine receptor D4 gene variant (4/4 variant; this gene is may play a role in attention-deficit/hyperactivity disorder [ADHD]) with effects on continuous performance testing among 179 Korean children with ADHD.~~

COMMENT: p. 270, line 15. DEHP or MEHP "did not alter the relationship between DEHP exposure and atopic dermatitis". What relationship? Table 2-9 says there was no relationship! Why was this finding not mentioned in 2.11 or 2.14.

RESPONSE: *This paragraph was fully revised for clarity (as seen below) and to address reviewer comments. The Wang and Karmaus (2015) study did not meet the selection criteria for epidemiological data outlined in Table B-1; therefore, health effects sections (e.g., Section 2.11, 2.14) do not contain data from this study.*

Section 3.2, Children and Other Populations that are Unusually Susceptible (Genetic Polymorphisms Altering Susceptibility): The potential for increased susceptibility to DEHP in individuals with ~~L~~loss-of-function filaggrin gene (FLG) variants has also been evaluated (filaggrin is an epidermal protein important to maintaining normal skin function, and its loss may enhance absorption of xenobiotics or allergens). No relationship between DEHP and atopic dermatitis was observed in individuals with or without FLG variants (Wang and Karmaus 2015). Additionally, ~~did not alter the relationship between DEHP exposure and atopic dermatitis, or change reproductive hormone levels or semen quality parameters, nor was~~ internal body burden of DEHP (as measured by urinary metabolite levels) was not altered in persons with FLG ~~these~~ variants (Joensen et al. 2014~~; Wang and Karmaus 2015~~).

COMMENT: p. 278, line 19. Suggest changing "2–30-fold " to "2 to 30-fold" for clarity.

RESPONSE: *See revised text below.*

Section 3.4 Interactions with Other Chemicals (Interactions Potentially Influencing Developmental Toxicity): The addition of the caffeine to the treatment using equimolar quantities of 2-ethylhexanol and 2-ethylhexanoic acid at doses half of the molar quantity used for DEHP resulted in ~~2–30~~ 2- to 30-fold increases in the dead and malformed fetuses and malformed survivors, but only minor decreases in the fetal weights.

COMMENT: p. 284, footnote. The uncertainty over the water solubility of DEHP is an important issue requiring elaboration. How can estimate of such a basic physical property span three orders of magnitude?

RESPONSE: *Poorly soluble substances such as DEHP have a great deal of uncertainty in their final reported water solubility and log K_{ow} values. The shake flask method (OECD 105) may lead to the formation of emulsions and the potential overestimation of solubility. The "slow-stir" method is the preferred method for measuring poorly soluble substances. Furthermore, solubility in pure water may differ significantly than the solubility in more environmentally relevant media. The footnote has been revised as seen below.*

> Section 4.2, Physical and Chemical Properties (Table 4-2, footnote): [a]The solubilities of DEHP in distilled water that have been determined both experimentally and theoretically vary between 1.1 and 1,200 µg/L (Staples et al. 1997). The highest values are likely to be overestimated as measurements that used the traditional shake flask method often led to the formation of emulsions. The value of 41 µg/L was the lowest experimentally derived value for the solubility of DEHP in distilled water. Yet, estimation models, SPARC and EPIWIN, provided solubility estimates of 2.6 and 1.1 µg/L, respectively (Staples et al. 1997), whereas Ellington (1999) found the chemical DEHP analog, dioctylphthalate, to have a solubility of 0.51 µg/L using the slow stir method. Letinski et al. (2002) determined DEHP solubility using the slow stir technique and reported a value of 1.9 µg/L in sterilized well water at 20°C.

COMMENT: p. 285. Map is wholly inadequate visual representation for geographically smaller states.

RESPONSE: *The map, Figure 5-1, is a template visual used in all ATSDR profiles. ATSDR will consider this Reviewer's comments in future revisions of the profile guidance.*

COMMENT: p. 285. Same criticisms as in Introduction. (Same text, actually.)

RESPONSE: *Based on the text in Section 5.1, ATSDR assumes that the Reviewer is indicating the p. 2, line 5 comment that appears in Section 1.1 (Overview and U.S. Exposures) as no annotated comments were received from this Reviewer relative to the introduction in Section 2.1. Revisions were made as seen below.*

> Section 5.1, Overview: The most likely route of exposure for the general public to DEHP is through ingestion of food, inhalation or ingestion of house dust, and dermal contact with consumer products containing DEHP. Occupational exposures may be significant in some settings. However, the highest DEHP exposures result from medical procedures.

COMMENT: Section 5.3. No information is provided on liberation of DEHP from burning materials, which is a concern with structural fires, occupational health, and emergencies.

RESPONSE: *Data pertaining to DEHP release from fires were added Section 5.3.1 and data pertaining to firefighters were added to Section 5.7.*

> Section 5.3.1, Air: DEHP may also be released into the air from burning domestic materials that still contain this compound from legacy use as a fire retardant, such as clothing and furnishing (Alexander and Baxter 2016; Lacey et al. 2014). DEHP detected on firefighter protective clothing has been attributed to release of semi-volatile toxic combustion products during structural fires (Alexander and Baxter 2016; Lacey et al. 2014).

Section 5.7, Populations with Potentially High Exposures: Firefighters and other emergency workers are also at a greater risk of DEHP exposure during structural fires due to potential release of DEHP from burning materials (Alexander and Baxter 2016; Lacey et al. 2014).

COMMENT: p. 335, line 14. This is a very peculiar statement in a scientific document. The word "foreign" is disturbing. Better: "Because much of the current literature on DEHP contamination of foodstuffs comes from outside the United States or does not reflect exposures of US residents, it is uncertain whether and for which product this information can be used in US-centered exposure or risk calculations. Examples include …"

RESPONSE: *The text, as seen below, was revised in a manner consistent with the Reviewer's suggestion.*

Section 5.6, General Population Exposure: Much of the current literature on DEHP contamination of foodstuffs ~~is foreign~~ comes from outside the United States or does not reflect typical exposures of U.S. consumers; ~~not typically associated with consumer exposures~~ therefore, it is uncertain whether and for which products this information can be used in U.S.-centered exposure or risk calculations ~~how applicable this information is to U.S. exposures; for example~~. Examples of available data include . . .

COMMENT: p. 336, line 2 – 4. It seems peculiar to imply that a visitor to a hospital would be exposed to DEHP in medical supplies. Better: "However, people who require only occasional medical care for conditions that do not require intravenous administration of fluids or medication, the use of medical devices, the use of invasive medical procedures, or instrumentation are exposed to much less than people with chronic conditions who require regular treatment or use medical devices."

RESPONSE: *This statement was intended to indicate that individuals who are treated infrequently in the hospital are at lower risk than individuals requiring regular treatments. It was not intended to imply that a visitor to a hospital would be exposed. The text was revised accordingly in a manner consistent with the Reviewer's suggestion (see below).*

Section 5.6, General Population Exposure: However, people who require only occasional medical care for conditions that do not require intravenous administration of fluids or medication, the use of medical devices, the use of invasive medical procedures, or instrumentation have a lower risk of exposure than people with chronic conditions who require regular treatment or use of medical devices. ~~However, the general population making infrequent hospital visits would not be at as much risk for exposure as people with certain medical conditions requiring regular~~ treatments ~~(see~~ Individuals with chronic conditions are discussed in Section 5.7 (Populations with Potentially High Exposures).

COMMENT: p. 337, line 3. "Offsite environment"? That is a new term, not in glossary, not in common use, and rather clunky. Substitute "into the ambient environment."

RESPONSE: *The text was revised as suggested (see below).*

Section 5.6, General Population Exposure: It is further anticipated that use facilities where DEHP is actively used, such as DEHP production or PVC manufacturing facilities, will emit more DEHP ~~to the offsite environment~~ into the ambient environment (e.g., through air-borne particulates or water) than storage or disposal facilities because of the tendency of DEHP to sorb to organic matter in the soil or sediment

COMMENT: p. 342, line 1. "…of the DEHP introduced into the infants…." Is this based on a calculation of exposure from what is eluted from tubing compared to what is recovered, or is it somehow measured? Must clarify. Also, phrasing "introduced into" implies intent and that is incorrect here.

RESPONSE: *No details on how the amount eliminated in the waste blood was calculated were provided by the study author. The study authors noted they obtained "additional samples" from the three infants for which the elimination in waste blood was reported. The text was revised, as shown below, to indicate this uncertainty and avoid the phrase "introduced into".*

Section 5.6, General Population Exposure: ~~They also noted~~ The study authors reported that for three infants, DEHP eliminated in the waste (exchanged) blood accounted for 12.5, 22.9, and 26.5% of the DEHP accumulated during transfusions, respectively ~~introduced into the infants was eliminated in the waste (exchanged) blood~~ (further details on this analysis were not available).

COMMENT: p. 348. This discussion confuses "data needs" with "data gaps", in my opinion. Information on inhalation exposure, whether acute or chronic, is not likely to be a limiting factor in practice in constructing a risk assessment for human exposure to phthalates. Goven other uncertainties of much greater magnitude, many of the gaps discussed are not critical.

RESPONSE: *As stated in the introduction Section 6.2, Identification of Data Needs, a data need is defined as "substance-specific information necessary to conduct comprehensive public health assessments," while any substance-specific information missing from the literature is defined as a data gap. For the purposes of the profile, data needed for hazard identification and derivation of MRL values are the primary focus. While inhalation is not the primary route of DEHP exposure, there is potential for human exposure via the inhalation route, so inadequate information for derivation of acute- or chronic-duration inhalation MRLs constitutes a data need with regard to this profile.*

COMMENT: p. 349, line 8. Disagree! The basic issue of water solubility is unresolved.

RESPONSE: *Revisions were made as seen below.*

Section 6.2, Identification of Data Needs (Physical and Chemical Properties): ~~The~~ Most of the physical and chemical properties of DEHP are sufficiently well characterized to allow estimation of its environmental fate and transport profile. On this basis, it does not appear that further research in this area is required. However, the experimental and theoretical water solubility values for DEHP differ by several orders of magnitude (1.1–1,200 µg/L). Additional experimental data are needed to decrease uncertainty in this value, particularly experiments using the slow-stir method.

COMMENT: p. 351, line 14. Revise sentence to: "Although much is known about historical exposure of children to DEHP, little is known about current exposure levels in children since the chemical has been withdrawn from many uses and products."

RESPONSE: *The text was revised as suggested (see below).*

Section 6.2, Identification of Data Needs (Exposures of Children): Although much is known about historical exposure of children to DEHP, little is known about current exposure levels in children since the chemical has been withdrawn from many uses and products ~~Little is known about exposures of children for DEHP~~.

COMMENT: p. 361, line 15. Suggest adding: ”Given current restrictions in the US, exposure assessment may require revisiting with greater emphasis on medical exposures in child care or treatment.”

RESPONSE: *The suggested sentence was added at the end of the paragraph discussing data needs for exposure in children (see below).*

> Section 6.2, Identification of Data Needs (Exposures of Children): Given current restrictions in the United States, exposure assessment may require revisiting with greater emphasis on medical exposures in child care or treatment.