DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR GLYPHOSATE (First Round of Peer Review)

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

September 2018

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

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Reviewers submitted files of the draft Toxicological Profile for Glyphosate with general comments and responses to ATSDR charge questions. For each Reviewer, comments are identified by file page number and heading associated with a particular comment. Where multiple comments were provided within a common heading, they are additionally identified by comment number. For example, Reviewer #1 submitted a comment regarding the lack of a statement on glyphosate-induced salivary gland effects. This comment is identified under the heading Chapter 2: Health Effects, comment #1, and page 2 of the file submitted by Reviewer #1. Two of the reviewers submitted comments and/or suggested text revisions on annotated pages of a file containing the Toxicological Profile for Glyphosate (draft 3 for peer review). Suggestions that were editorial and/or stylistic nature were addressed at the discretion of ATSDR. Other suggestions that required a formal response are identified by Chapter, Section, page, and/or line number associated with the file of annotated comments provided by each Reviewer separately under the heading "**Specific Comments on Annotated Pages of the Toxicological Profile for Glyphosate,**" following the General Comments (the pages and line numbers on the annotated pages were identified using the "show only comments and formatting in balloons" review format). For example, Reviewer #1 submitted a comment on P12, L18-19, which refers to page 12 lines 18-19 of the file submitted by Reviewer #1.

Comments provided by Reviewer #1:

General Comments

Comment #1, page 1: The Reviewer stated "Glyphosate and its formulation products are important commercial products and are extensively used. Given the recent concerns about possible adverse health effects resulting from glyphosate exposure, the drafting of a Toxicological Profile on Glyphosate by the ATSDR is timely and can help address public concerns. There are, however, a number of somewhat unique challenges in reviewing the epidemiological and toxicological data related to glyphosate. One is that glyphosate is produced in different forms and is almost always used as a formulation product. There are a large number of formulation products with differing ingredients that have been or are being used, and significant differences in toxicity have been seen in some cases between glyphosate and its formulation products. As a result, the ATSDR has chosen to review glyphosate and its formulation products separately in the draft Profile."

RESPONSE: *No response is necessary.*

Comment #2, page 1: The Reviewer stated "The second challenge is that ATSDR has a policy to use only primary references that have been peer reviewed and, if they are not already publicly available, to make the reviewed materials available to the public. Hundreds of studies on glyphosate and its formulation products have been performed. Many of these, possibly the majority, are confidential unpublished guideline studies that have been submitted to regulatory organizations as part of pesticide registration packages. As a result, only a fraction of the total studies on glyphosate and its formulation products were available to the ATSDR, for use in writing the Profile. Other regulatory agencies such as the USEPA, EFSA and JMPR have had access to both the published and confidential unpublished studies. These agencies also do not have a policy that the reviewed studies be made publicly available. As a result, large numbers of unpublished guideline studies on glyphosate have played major roles in the regulatory agency assessments. As indicated above, in most cases, the ATSDR did not have access to the unpublished studies. However, it does have access to summaries that have been generated by the regulatory agencies."

RESPONSE: *No response is necessary.*

Comment #3 page 1: The Reviewer stated "Similarly, groups of industry-funded experts have reviewed many unpublished studies on glyphosate and have published detailed summaries in the peer-reviewed literature. In some cases (e.g. for Kier and Kirkland (2013) the information has been mentioned in the Profile. In others, such the article by Greim et al., (2015), the summarized studies don't appear to be included."

RESPONSE: *ATSDR does not typically rely upon summaries of studies from secondary sources, particularly for health effects data. In some cases, secondary sources for genotoxicity results are mentioned. ATSDR has also presented conclusions from available secondary sources regarding carcinogenicity evaluations. Greim et al. (2015) was added to the list of secondary sources evaluating the potential carcinogenicity of glyphosate.*

Comment #4, pages 1-2: The Reviewer stated "Decisions about when to use these summaries may not always be straightforward and may require judgment calls. From my perspective, the authors of the draft Profile have done a skillful job at trying to evaluate the publicly available studies, the unpublished ones

that they have been able to obtain from the USEPA, and incorporate summary information from regulatory agencies and expert panels. However, there are gaps in the coverage of certain topics and differences in the evidence that can be weighed to reach a conclusion. In some cases, information from some regulatory agency evaluations and industry-sponsored expert summaries has been included and in other cases, it has not. In my edits and in the comments below, I have pointed out areas where I think improvements can be made in this and other areas. However, overall, I believe that the ATSDR has done a good job given the constraints associated with its policy. I do believe that the information about the limited accessibility to a large number of unpublished studies should be communicated to the readers of the Profile, preferably early in the document. I have added some suggested language in the Preface, but it or a similar statement could be placed elsewhere."

RESPONSE: *Responses to the issues described in this paragraph are provided in the portion of this Disposition of Peer Review Comments identified as "Specific Comments on Annotated Pages" provided by the Reviewer, found at the end of the General Comments section.*

Chapter 1: Relevance to Public Health

Comment #1, page 2: The Reviewer stated "The Profile evaluates glyphosate technical and its formulation products separately. While this makes some aspects of the review simpler, it may be seem duplicative to some readers and limits the coverage in some areas of the document. It also may be seen as not adequately addressing public concerns."

RESPONSE: *Separate presentation within each health endpoint is standard procedure for ATSDR toxicological profiles on pesticides. It is intended to allow the reader to better evaluate similarities and differences between an active ingredient such as glyphosate and formulations of pesticides that contain active ingredients and other potentially toxic substances, etc.*

Comment #2, page 2: The Reviewer stated "I am not aware of health effects caused in humans by glyphosate technical."

RESPONSE: *No response is necessary.*

Comment #3, page 2: The Reviewer stated "In the absence of convincing evidence indicating otherwise, I believe that the results seen in animals should be considered relevant to humans. Many of the glyphosate studies were conducted at high to very high doses. The results may not be relevant to humans exposed to much lower levels but this is related to dose rather than interspecies differences."

RESPONSE: *No response is necessary.*

Comment #4, Page 2: The Reviewer stated "The exposure conditions have only been described in very general terms. I recommend that a sentence or a paragraph be added explaining that due to its widespread usage, low levels of glyphosate can be found in many different types of food."

RESPONSE: *See response to this comment in the annotated pages section, found at the end of the General Comments section.*

Comment #5, page 2: The Reviewer stated "According to the text, MRL values have not been derived, in part due to database deficiencies. I recommend that the agency consider deriving provisional MRLs or something similar as they would provide the public with a reasonably safe benchmark to which it could refer. They could be provided with a notice of potential deficiencies and that at higher doses, glyphosate in combination with other ingredients in the formulation products have been reported to be more toxic than glyphosate itself. I do see that MRL values for glyphosate technical are shown in Figure 2-3 but I haven't found them discussed in the text. I note that those presented are similar to the ADI values generated by the JMPR and others, indicating some consistency across authoritative bodies in the evaluation of studies."

RESPONSE: *Depictions of MRL values in Figure 2-3 were in error; they have been removed. Data on glyphosate-based formulations (GBFs) are not sufficient to derive MRLs. The concentration of glyphosate in GBFs varies. GBFs also contain other additives (e.g., surfactants), and the data indicate that these additives may be more toxic than the active ingredient. In addition, much of the information on the GBFs is proprietary. Human exposure to GBFs via its use in weed control includes exposure to all substances in GBFs. No MRLs were derived for GBFs due to the wide variation in glyphosate content and surfactants used in various GBFs and the fact that surfactants can contribute to the toxicity of GBFs. However, the general population may also be exposed to glyphosate and/or its breakdown products by ingesting food or water in which glyphosate is detected. Therefore, health effects data from oral exposure to glyphosate technical are considered relevant to potential derivation of oral MRLs for glyphosate. ATSDR is considering whether to derive oral MRLs for glyphosate based on animal data for glyphosate technical; the results of this consideration will be applied to future drafts of the Toxicological Profile for Glyphosate.*

Chapter 2: Health Effects

Comment #1, pages 2-3: The Reviewer stated "Studies of the health effects of glyphosate and its formulation products in humans and animals are presented in tables and figures. Key details are provided in the tables with additional information presented in the text as appropriate. The coverage seems to be appropriate for this type of document. The summary of the effects in major organ systems seems to be fitting. Effects on the salivary gland have not been included within the gastrointestinal tract category. I believe that they should be as changes affecting this organ were the basis for the point of departure used by the JMPR to set its ADI."

RESPONSE: *Effects on the salivary gland were added to Chapter 2 under gastrointestinal effects.*

Comment #2, page 3: The Reviewer stated "Potentially serious ocular effects that have been seen in some unpublished studies were not seen in the studies that the ATSDR reviewed and as a result, are not reflected in the document. Both ECHA (2017) and JMPR (2017) have raised concerns about ocular effects seen in some animal experiments. I suggest that the agency conclusions regarding these effects be mentioned in the Profile as they could have important public health ramifications."

RESPONSE: *Some text was added to the ocular effects section along with conclusions of European Chemicals Agency (ECHA 2017) and Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (FAO and WHO 2016).*

Comment #3, page 3: The Reviewer stated "Under the Developmental effects and Endocrine effects bullet points, effects that were reported to occur at unusually low doses are listed. Both of the studies

seem suspect and the results seem anomalous to me. The fact that effects were not seen in multigenerational studies, at least with glyphosate, until much higher doses makes one wonder about the potential biological significance of these reported changes. I recommend that the studies be evaluated again to determine whether they warrant such a prominent position in the document."

RESPONSE: *The studies were re-evaluated. However, although the lowest-observed-adverse-effect levels (LOAELs) in these studies were lower than no-observed-adverse-effect levels (NOAELs) in other studies, there was no apparent scientific reason to discount the results.*

Comment #4, page 3: The Reviewer stated "Many on the studies in Table 2-1 are not readily available and as a result, the entries could not be checked for accuracy."

RESPONSE: *Although primary studies were not available in some cases, the Endnote file did contain cleared reviews (Data Evaluation Records) from EPA that were considered adequate for the purpose of this toxicological profile.*

Toxicity – Quality of Human Studies

Comment #1, page 3: The Reviewer stated "The human studies that were identified seem to have been adequately designed. As indicated all exposures involved glyphosate formulations. To my knowledge, there were no reports of exposure solely to glyphosate technical. Given the number and nature of the human studies, the results have primarily been presented in tabular form and briefly summarized in the text. There is little discussion of the study limitations, statistical analyses, and conclusions. LOAELs and NOAELs have generally not been provided for the human studies. Given the nature of the Profile and most of the studies, I consider the approach taken by the ATSDR to be appropriate."

RESPONSE: *No response is necessary.*

Comment #2, page 3: The Reviewer stated "Direct exposures have occurred to residents living in areas of Columbia and Ecuador where glyphosate formulations have been sprayed over their communities in government-sponsored coca eradication programs (Paz-y-Minos et al., 2007 and 2011). The residents have reported a variety of adverse effects. Whether these effects are directly related to glyphosate, other ingredients in the applied formulation product or psychological stress due to living in the spray zone is uncertain. It should also be noted that the application rate described in the Paz-y-Minos et al. (2007) study has been reported to be 20 higher than the recommended application rate (Kier, 2015). These studies should be reviewed and included at the appropriate places in the Profile if it is determined that inclusion is warranted."

RESPONSE: *The study results of Paz-y-Minos et al. (2007, 2011) are included in the toxicological profile.*

Toxicity – Quality of Animal Studies

Comment #1, page 4: The Reviewer stated "As indicated above, there are large numbers of animal studies on glyphosate and its formulation products that are not in publicly available literature. Within its policies, the ATSDR has done a good job identifying appropriate studies to review. For the most part, the species identified, the statistical analysis and the conclusions appear to be appropriate. As noted above,

many of the studies used by the ATSDR were not readily available for review and have not been checked for accuracy. When results seemed to be unusual, I have flagged them for re-review. For example, this was done for several of the reported studies (e.g. on developmental and endocrine effects) that had atypically low LOAEL values. These seem suspect to me and should be re-examined for quality. Even if acceptable, if studies are concluded to be an anomalous, they should be described as such in the text."

RESPONSE: *See responses to specific comments on the annotated pages, found at the end of the General Comments section.*

Comment #2, page 4: The Reviewer stated "The major types of toxicological effects have been adequately reviewed. For some types of effect, there are not very many studies in the public domain. As indicated above, potentially serious ocular effects have been seen in some (but not all) unpublished animal studies and these are not reflected in the document. I recommend that the ECHA (2017) and JMPR (2017) conclusions regarding these effects be mentioned in the Profile as they could have important public health ramifications."

RESPONSE: *See responses to specific comments on the annotated pages found at the end of the General Comments section.*

Comment #3, page 4: The Reviewer stated "In particular, very few acceptable animal cancer bioassays are available in the publicly available literature. Many more exist as industry-sponsored unpublished studies. Some of these have been accessed by through EPA reviews and documents. An industry-sponsored review of 14 unpublished chronic/carcinogenicity rodent studies has recently been published by Greim et al. (2015). Whether these summaries provide sufficient details and are considered to be sufficiently reliable to allow their inclusion in the Profile is a decision that the ATSDR should make. The summaries might also be compared with those of the EPA (2015, 2016), JMPR (2017) and EFSA (2015; Tarazona et al., 2017) which also had access to the primary unpublished documents before making a decision on the reliability of the information."

RESPONSE: *Conclusions of Greim et al. (2015), ECHA (2017), the Australian Pesticides and Veterinary Medicines Authority (APVMA 2017), Health Canada (2017), and the New Zealand Environmental Protection Authority (NZEPA 2016) were added to the cancer discussion.*

Comment #4, page 4: The Reviewer stated "A sizable number of genotoxicity studies in the publicly available literature are not listed in the tables. In addition, the review by Kier and Kirkland (2013) provides key information on a large number of industry-sponsored unpublished studies. Since these studies are mentioned, albeit briefly, in the text, I would recommend considering them for inclusion in the tables as well."

RESPONSE: *The unpublished studies that were only available to ATSDR as summary information from review articles were not added to the genotoxicity tables because the studies could not be independently evaluated.*

Comment #5, pages 4-5: The Reviewer stated "Below are conventional genotoxicity studies on glyphosate and its formulation products that can be found in publicly available literature but which are not listed. Whether or not these meet ATSDR's criteria for quality needs to be determined.

Amer SM, Aly FAE, Farghaly AA, Ibrahim AAE (2006). In vitro and in vivo evaluation of the genotoxicity of the herbicide glyphosate in mice. B Natl Res Cent (Cairo). 31:427–46. Note: This study was included by the JMPR but considered to be anomalous. It was judged to be unacceptable by USEPA.

Chruscielska K, Graffstein B, Szarapinska-Kwaszewska J, Brzezinski J, Kalhorn D (2000b). Glyphosate: Evaluation of chronic activity and possible far-reaching effects. Part 2. Studies on mutagenic activity. Pestycydy (Warsaw). 3–4: 21–5.

Gohre K, Casida JE, Ruzo LO (1987). N-Oxidation and cleavage of the amino acid derived herbicide glyphosate and anilino acid of the insecticide fluvalinate. J. Agric. Food Chem. 35:388-392.

Heydens WF, Healy CE, Hotz KJ, Kier LD, Martens MA, Wilson AG et al. (2008). Genotoxic potential of glyphosate formulations: Mode-of-action investigations. J Agric Food Chem. 56(4):1517–23.

Koller VJ, Furhacker M, Nersesyan A, Misik M, Eisenbauer M, Knasmueller S (2012). Cytotoxic and DNA- damaging properties of glyphosate and Roundup in human-derived buccal epithelial cells. Arch Toxicol. 86:805-13. [DNA strand breaks]

Lueken A, Juhl-Strauss U, Krieger G, Witte I (2004). Synergistic DNA damage by oxidative stress (induced by H2O2) and nongenotoxic environmental chemicals in human fibroblasts. Toxicol Lett. 147:35–43.

Ming Z, Ting H, Yiping Y, Caigao Z, Lan G, Wang A et al. (2014). Cytotoxicity of glyphosate to GC-1 mice spermatogonium and antagonistic effects of N-acetylcysteine. Asian J Ecotoxicol. 9(1):159–66. doi:10.7524/AJE.1673-5897. 20130906001.

Piesova E (2004) The influence of different treatment length on the induction of micronuclei in bovine lymphocytes after exposure to glyphosate. Folia Veterinaria. 48(3):130–4.

Piesova E (2005). The effect of glyphosate on the frequency of micronuclei in bovine lymphocytes in vitro. Acta veterinaria (Beograd). 55(2):101–9. doi: 10.2298/AVB0503101P.

Sivikova K, Dianovsky J (2006). Cytogenetic effect of technical glyphosate on cultivated bovine peripheral lymphocytes. Int J Hyg Environ Health. 209:15–20.

RESPONSE: *Most of these studies were already presented in the toxicological profile. The remaining studies were reviewed and relevant information was added to the toxicological profile.*

Comment #6, page 5: The Reviewer stated "In addition, there are a large number of genotoxicity studies that have been conducted using unconventional organisms (plants, frogs, fish, caiman, etc.), often in non-standard bioassays. A fairly comprehensive listing of these (~70 assay results) can be found as an appendix of the JMPR (2017) monograph. Most, if not all, of these are in publicly available literature. The ATSDR needs to decide whether it is appropriate to add them to its tables and use them in the evaluation. IARC used them in its evaluation. JMPR listed them in an appendix but gave them relatively little weight in its evaluation. I don't believe these were included in the USEPA's evaluation."

RESPONSE: *It is common practice for ATSDR to rely on genotoxicity testing with conventional test systems such as bacteria, drosophila, mammalian cell lines, and mammalian species in vivo. For genotoxicity testing of glyphosate, ATSDR relied on primarily on information provided to ATSDR by EPA and other publicly-available primary study results.*

Comment #7, pages 5-6: The Reviewer stated "For in vivo genotoxicity studies on glyphosate, it is important that the route of exposure be shown in the table or that oral studies be listed separately from intraperitoneal (ip) injection studies. I would recommend that the study results be described in the text by route of administration. The oral studies are almost all negative whereas the results of studies where glyphosate or its formulation products were administered by ip injection show mixed, frequently positive, results. This should be factored into how the studies are weighed for human relevance (see below)."

RESPONSE: *The in vivo tables were revised to separately depict route of exposure.*

Comment #8, page 6: The Reviewer stated "In addition, some context should be given to the ip injection studies. The LD50 listed in the peer-reviewed HSDB database is 135 mg/kg bw for the mouse and 238 mg/kg bw for the rat. The doses administered by ip injection in a number of the genotoxicity studies exceeded these LD50 values and so it is not surprising that non-specific genotoxic effects such as DNA strand breaks and oxidative damage have been seen."

RESPONSE: *The following statement was added to the genotoxicity section that summarized results for glyphosate technical: "It should be noted that intraperitoneal injection studies typically employed lethal dose levels; a positive result at such high dose levels does not necessarily indicate potential for genotoxicity at doses relevant to human exposure."*

Comment #9, page 6: The Reviewer stated "The Profile largely lists the various genotoxicity studies but does not draw overall conclusions from the results. This keeps the report from being controversial and may be advisable given that the ATSDR only has access to a portion of the total genotoxicity information on glyphosate. Another approach is to draw stronger overall conclusions. If the ATSDR decides to take that approach, I recommend that the genotoxicity studies be evaluated and weighted to reach a conclusion as to whether or not an agent induces cancer or heritable effects through a mutagenic mode of action. The major factors considered for study acceptability and weighting that were used by the JMPR in reaching its conclusions on genotoxicity can be found in Eastmond (2017). These may be useful and adapted for ATSDR evaluations."

RESPONSE: *ATSDR did not implement a weight-of-evidence approach to genotoxicity data because much of the primary genotoxicity data were not available to ATSDR. The following text was added to the genotoxicity section to summarize the genotoxicity findings:*

"DNA damage in human fibroblast cells and peripheral blood lymphocytes were the most frequently reported clearly positive results from available in vitro assays that employed glyphosate technical. From available in vivo assays that employed glyphosate technical, DNA damage in mouse kidney and liver was the most frequent positive result. Summaries should be interpreted with caution because the genotoxicity of glyphosate technical was assessed based on a limited number of primary results available to ATSDR."

"DNA damage in human cells was the most frequently reported clearly positive results from available in vitro assays that employed glyphosate formulations. However, comparison of results across available studies was precluded due to lack of information regarding the composition of the various formulations tested. From available in vivo assays that employed glyphosate formulations, DNA damage in mouse kidney and liver was the most frequent positive result. Summaries should be interpreted with caution because the genotoxicity of glyphosate technical was assessed based on a limited number of primary results available to ATSDR."

Metabolism and Toxicokinetics

Comment #1, page 6: The Reviewer stated "In the description of several of the studies in which glyphosate was administered orally, it describes elimination through the urine and feces. Most of that recovered in the feces appears to be unabsorbed glyphosate. The iv portion of the NTP (1992) study indicates that almost all of the glyphosate that reaches the blood is excreted in the urine. This implies that most of the glyphosate seen in the feces in the oral experiments is unabsorbed glyphosate. This conclusion is supported by a small (one rat) study briefly mentioned by Gohre et al. (1987) and a larger one described in JMPR (2004) that indicate that there is very little biliary excretion. I recommend that this information be added to the text."

RESPONSE: *See response to this comment in the annotated pages section found at the end of the General Comments section.*

Comment #2, page 6: The Reviewer stated "Gohre et al. (1987) also briefly report that they observed no metabolic products or binding to albumin when glyphosate was incubated with rat liver post-mitochondrial supernatant. This is consistent with the very low levels of AMPA detected in the in vivo studies. I might mention that after ip injection, Ford et al. (2017) reported that approx. 4% of the administered glyphosate was recovered in the liver as glyoxylate, an electrophilic and protein-reactive species. Glyoxylate is also an endogenous metabolite present normally in the liver (Benham eta al., 2006)."

RESPONSE: *Results from Ford et al. (2017) were added to the metabolism section of the toxicological profile.*

Comment #3, page 6: The Reviewer stated "The results of one additional human biomonitoring study should be considered for addition. The study is:
Koureas M, Tsezou A, Tsakalof A, Orfanidou T, Hadjichristodoulou C (2014). Increased levels of oxidative DNA damage in pesticide sprayers in Thessaly Region (Greece). Implications of pesticide exposure. Sci Total Environ. 496:358–64."

RESPONSE: *Koureas et al. (2014) reported a significant association between glufosinate ammonium (not glyphosate) and increased 8-OHdG levels (indicator of oxidative DNA damage) in blood samples from pesticide applicators. There was no significant association for glyphosate. Therefore, the results were not included.*

Levels of Significant Exposure (LSE) Tables and Figures

Comment #1, page 7: The Reviewer stated "The LSE tables and figures appear to reflect the publicly available data and are consistent with the information in the text. They are clear and understandable. I consider them to be one of the best components of the ATSDR Profiles. The Users Guide is helpful as well, although since it is at the end of the Profile, I am not sure many readers will see it. I recommend that a reference to it be placed in a footnote in at least the first LSE table and LSE figure. For the studies that I checked, the categorizations of "less serious" and "more serious" seemed appropriate."

RESPONSE: *A statement referring the reader to Appendix C for information to aid in the interpretation of the tables and figures for LSEs is included in the introduction to Chapter 2.*

Evaluation of Text

Comment #1, page 7: The Reviewer stated "Most studies are only briefly discussed in the text. The endpoints all seem to be relevant to both animals and humans. There are a few studies (indicated in the document and above) that strike me as suspect. I have recommended that they be re-reviewed for quality and consistency with other studies. If they continue to be anomalous, that should be indicated in the text. While there are bottom line statements, I believe that the authors have been cautious and avoided making strong and firm statements. This is probably a good idea as the authors are working from a limited data set for many of the endpoints. The conclusions seem reasonable except where indicated in my edits of the document. I don't recall much focus on dose-response relationships. Given the co-exposures in most human studies and lack of good exposure data, most of the conclusions about possible or likely human health effects have come from the animal data. This is appropriate from my point of view."

RESPONSE: *No response is necessary.*

Mechanisms of Action

Comment #1, page 7: The Reviewer stated "This section is missing from the draft Profile. I recommend that a short mechanism of action section (3.5 in other Profiles) be added. In the IARC (2015) evaluation, two potential modes of action were identified for carcinogenicity. One was genotoxicity which is covered in the Profile. The other was oxidative stress. I would recommend that it be covered briefly beginning with the studies mentioned in the IARC evaluation. I would also bring in information from the new article by Bus which critiques the evidence for the involvement of reactive oxygen species in glyphosate toxicity.

RESPONSE: *A Mechanisms of Action Section (Section 2.21) was added to the profile.*

Comment #2, page 7: The Reviewer stated "In addition, I would recommend adding a discussion on the information provided in the Ford et al. (2017) article. Although it is a single study that used ip injection at high doses, it identified a reactive protein-binding metabolite formed from glyphosate and potential targets that may explain some of glyphosate's toxic effects, such as the genotoxic effects seen following ip injection."

RESPONSE: *Results from Ford et al. (2017) were added to the metabolism section of the toxicological profile as evidence of glyphosate metabolism in mammals and to Section 2.9 (Hepatic) as evidence of possible mechanisms of action for hepatic toxicity.*

Ongoing Studies

Comment #1, pages 7-8: The Reviewer stated "I am aware of a couple of additional groups that are conducting research into glyphosate and its formulation products. These are indicated in the text. The NTP glyphosate research plan can be found on its website at: https://ntp.niehs.nih.gov/results/areas/glyphosate/index.html. A new article on the Ramazzini Institute's ongoing glyphosate studies can be found at:

http://www.reuters.com/article/us-health-europe-glyphosate-idUSKBN17F0S1

RESPONSE: *A statement was added regarding the NTP ongoing investigation. However, a statement regarding studies initiated at the Ramazzini Institute was not added because available information was located only from news agencies and not from the institute itself or any other reliable scientific source.*

In a separate comment file, Reviewer #1 peer-reviewed the following 3 unpublished sources for information in the Toxicological Profile for Glyphosate:

"Winfield Solutions submission to the USEPA dated Oct. 27, 2010. This consists of a form submitted the USEPA as part of the registration of a glyphosate formulation. The requested label was considered unacceptable but the product was unconditionally registered provided that some conditions were adhered to. It appears to be pretty standard label material. I might mention that I am not convinced that it serves as a valid reference for the information for which it is cited in the Profile.

Alferness (1993), an unpublished study (#GLYP-92-AM-04) labeled as Volume 2, performed by Zeneca Ag Products entitled, "TOUCHDOWN: Determination of Glyphosate and Aminomethylphosphonic Acid in Corn Grain, Corn Forage, and Corn Fodder by Gas Chromatography and Mass-Selective Detection". This appears to be a fairly standard guideline study describing a method to determine residues and glyphosate and AMPA in corn commodities. Some results of the analyses are also shown. I should mention that this is not directly in my area of expertise but in general, I consider GLP guideline studies to be of good quality. I have the some opinion about this study. The deviation from the GLP guidelines mentioned do not appear to be significant to me. This is a valid reference for its use in the Profile.

Pioneer (2006), an unpublished study performed by Pioneer Hi-Bred International, entitled, "Early food safety evaluation for a glyphosate N-acetytransferase protein: GAT4601". This is a report describing the use of DNA shuffling to develop a protein with glyphosate N-acetyltransferase activity that can be used to transform soy bean plants to regenerate their tolerance to glyphosate. The report also describes the results of some initial experiments on the immunogenicity and acute toxicity of the GAT4601 protein identified. The report appears to be of good quality and supports the statements in the Profile (after I made corrections)."

RESPONSE: *No response is necessary.*

Reviewer #1 Specific Comments on Annotated Pages of the Toxicological Profile for Glyphosate

FOREWORD

COMMENT: Piii, L15-22: The Reviewer stated "I think it is important that the information in these sentences be added to the first part of the document. The sentences can be modified and moved to another location but I think the key points need to be included." The Reviewer suggested that something similar to the following be added to the final paragraph of the FORWARD: "It should be noted that glyphosate and its formulation products are commercial products and that a large number of unpublished studies have been conducted to support their registration by the US EPA and other regulatory agencies. These studies are considered confidential business information and in most cases, were not available for review by the ATSDR and have not been included in the profile. These studies have been reviewed by the EPA, EFSA and JMPR as part of their risk assessments. In some cases, when other authoritative bodies (e.g. EPA) had

previously reviewed the studies or when ATSDR was provided access to the original reports, the studies have been included (after peer-review when appropriate)."

RESPONSE: *This information is considered to be adequately presented in the introduction to Chapter 2.*

CHAPTER 1. PUBLIC HEALTH STATEMENT

COMMENT: P12, L18-19: Regarding the statement "In 2007, U.S. agricultural use of glyphosate was approximately 82,800 tons and non-agricultural use of glyphosate was 9,300 tons (Battaglin et al. 2014), the Reviewer stated "I recommend updating this using 2014 usage as described in Benbrook (2016)."

RESPONSE: *The following was added: "In 2014, U.S. agricultural use of glyphosate was approximately 124,953 tons and non-agricultural use of glyphosate was approximately 13,260 tons (Benbrook 2016)."*

COMMENT: P12, L30-33: The Reviewer suggested adding information regarding the presence of glyphosate at low levels in a wide range of foods.

RESPONSE: *The suggested addition was made.*

COMMENT: P13, L1: The Reviewer indicated that the presence of glyphosate at hazardous disposal sites seems unlikely to be significant.

RESPONSE: *Although unlikely, one purpose of ATSDR Toxicological Profiles is to inform populations living in the vicinity of hazardous waste disposal sites.*

COMMENT: P13, L32: The Reviewer suggested adding information regarding glyphosate effects on the salivary gland.

RESPONSE: *The suggested addition was made.*

COMMENT: Figure 1-1; Table 2-1, and selected text in Chapters 1 and 2: The Reviewer suggested adding glyphosate effects on the salivary gland in the rat and mouse studies of NTP (1992).

RESPONSE: *The suggested addition was made.*

COMMENT: P16, L2-3: The Reviewer suggested emphasizing that gastrointestinal effects have frequently been observed in animal studies.

RESPONSE: *The suggested addition was made.*

COMMENT: P16, L25: The Reviewer stated "ECHA classified glyphosate as Serious Eye Damage Category 1 based on effects seen in some studies but not all. JMPR also indicated that glyphosate was moderately to severely irritating to the eyes of rabbits. Industry: believed this to be related to the acid

form and may not be seen with formulations; the effects were not seen when the eye was rinsed 1 hr after treatment."

RESPONSE: *The following statement was added: "According to EPA (1993), glyphosate is considered mildly irritating to the eye following ocular instillation."*

COMMENT: P17, L28-30: The Reviewer suggested that the USEPA evaluation of glyphosate carcinogenicity be added to the paragraph summarizing evaluations of other entities.

RESPONSE: *The following statement was added: "The EPA Integrated Risk Information System (IRIS 1989) classified glyphosate as Group D (not classifiable as to human carcinogenicity)."*

COMMENT: P19, Figure 1-2: The Reviewer suggested adding the LOAEL for salivary gland effects reported by NTP 1992 to text and the figure.

RESPONSE: *The suggested additions were made.*

COMMENT: P19, L12-13: The Reviewer stated "Direct exposures have occurred to residents living in areas of Columbia and Ecuador where glyphosate formulations have been sprayed over their communities in government sponsored coca eradication programs (Paz-y-Minos et al., 2007 and 2011). The residents have reported a variety of adverse effects. These studies should be reviewed and discussed at the appropriate places in the Profile if it is determined that inclusion is warranted."

RESPONSE: *The study results of Paz-y-Mino and coworkers are present in the profile in the genotoxicity section.*

COMMENT: P19, L18-22: The Reviewer questioned the findings of developmental and endocrine effects at a low dose of 5 mg/kg/day.

RESPONSE: *The study was re-examined and the dose of 5 mg/kg/day at which developmental and endocrine effects were observed is correct.*

COMMENT: P24, Figure 2-1: The Reviewer stated that the numbers in the bars should be explained; the Reviewer supplied the following text suggestion for the footnote: "The number of studies reporting on the specific outcome are shown in each bar."

RESPONSE: *Text was added to note that counts represent the number of studies examining an endpoint.*

COMMENT: P25, Figure 2-2: The Reviewer stated that the dark and light blue bars should be explained.

RESPONSE: *The legend was revised to more clearly identify human and animal studies by color code.*

COMMENT: P26, Table 2-1: The Reviewer stated that EPA 1992b and other EPA documents were not accessible for review.

RESPONSE: *The EPA documents are in endnote and should have been available to Reviewers.*

COMMENT: P29, Table 2-1: Regarding the NTP (1992) rat study, the Reviewer stated "A decrease in body weight was reported at the 25,000 ppm (1678 mg/kg) dose. If this is considered to be biologically significant, the NOAEL would be 811 mg/kg."

RESPONSE: *The magnitude of the body weight change at 1,678 mg/kg/day was less than 10% and was therefore considered not adverse.*

COMMENT: P37, Table 2-2: The Reviewer indicated that the body weight effects data from the Jasper et al. (2012) study appears suspect. The Reviewer stated "The variability within the controls and treatment animals seems minimal for 10 animals. I don't believe that major decreases in body weight gain have been seen in other studies until much higher doses were reached and the changes were not nearly as dramatic."

RESPONSE: *There is no apparent reason to discount the finding. At 500 mg/kg/day, animals actually lost weight. Differences between studies may reflect differences in animal species and strain, method of oral exposure, specific glyphosate formulation, etc.*

COMMENT: P38, Table 2-2: The Reviewer indicated that developmental and endocrine effects reported by Romano et al. (2010) seem anomalous given that effects were not seen in multigenerational studies until much higher doses had been administered.

RESPONSE: *As stated previously, the study was re-examined and the dose of 5 mg/kg/day at which developmental and endocrine effects were observed is correct.*

COMMENT: P42, L24: The Reviewer asked whether the 28.5% lower mean body weight actually refers to body weight gain.

RESPONSE: *The statement was corrected to note the lower mean body weight gain.*

COMMENT: P43, L7-9: The Reviewer suggested that the body weight result reported by Jasper et al. (2012) is anomalous and that one should be more cautious in the description of the effect.

RESPONSE: *As stated previously, there is no apparent reason to discount the finding. At 500 mg/kg/day, animals actually lost weight.*

COMMENT: P49, Table 2-4: The Reviewer was unsure of the meaning of the stated outcome from the study of Sathyanarayana et al. (2010).

RESPONSE: *The outcome was revised to state "Multiple regression estimates of change in birth weight (g) in relation to maternal self-reported glyphosate use (coefficient=4 g; 95% CI -40–48 g) indicate no significant association between birth weight and maternal use of glyphosate."*

COMMENT: P50, L2: The Reviewer stated "There is another study (Kumar et al., 2014) on the effects of glyphosate on airway inflammation that you might want to mention here."

RESPONSE: *The following was added: "Kumar et al. (2014) reported an inflammatory respiratory response (evidenced by increased eosinophil and neutrophil counts, mast cell degranulation, and production of IL-33, TSLP, IL-13, and IL-5) in anesthetized mice exposed intranasally to glyphosate."*

COMMENT: P52, L12-14: The Reviewer suggested adding the following text: "Small changes in hematological parameters were seen in both male and female rats in the 13 week NTP study (NTP, 1992). These were considered to be unremarkable and most likely due to mild dehydration."

RESPONSE: *The suggested addition was made.*

COMMENT: P53, L23: The Reviewer stated that the description of the Jayasumana et al. (2015) study is misleading. The Reviewer further stated "The study was a case-control study of patients with chronic kidney disease. The description should be changed to better reflect the study design."

RESPONSE: *The description was revised to note that it is a case-control study of patients with chronic kidney disease.*

COMMENT: P55, Section 2.12: The Reviewer stated "The JMPR concluded that glyphosate as moderately to severely irritating to the rabbit eye. ECHA has classified glyphosate as Serious Eye Damage Category 1."

RESPONSE: *The following was added: "According to FAO and WHO (2016), glyphosate was moderate to severely irritating to the rabbit eye. EFSA (2015) stated that glyphosate acid was a severe ocular irritant, but that salts of glyphosate do not require classification as ocular irritants."*

COMMENT: P56, L18: The Reviewer stated "The study by Kumar et al.(2014) on airway inflammation might also be included here."

RESPONSE: *The results from Kumar et al. (2014) were added to Section 2.14.*

COMMENT: P76, L22-24: The Reviewer suggested adding the following text: "Similar conclusions were reached by the European Chemicals Agency (ECHA 2017), the Australian Pesticides and Veterinary Medicines Authority (APVMA, 2017) and the New Zealand Environmental Protection Authority."

RESPONSE: *The suggested addition was made, pending copyright permission from the New Zealand Environmental Protection Authority.*

COMMENT: P76, L33 to P77, L2: Regarding the statement "Results from publicly-available *in vitro* and *in vivo* genotoxicity tests for selected glyphosate formulations are presented in Tables 2-12 and 2-13, respectively", the Reviewer stated "A sizable number of studies in the publicly available literature are not listed. They are listed in my General Comments."

RESPONSE: *The identified genotoxicity studies were reviewed and relevant information was added to the toxicological profile.*

COMMENT: P78, Table 2-11 and P80, Table 2-13: The Reviewer stated that studies in which glyphosate was administered orally should be distinguished from those administered by ip injection.

RESPONSE: *The table was revised to identify route of exposure for each study.*

COMMENT: P81, L25-26 and P83, L9-10: The Reviewer suggested describing results from *in vivo* tests separately by exposure route.

RESPONSE: *The text was revised to present results from oral studies followed by intraperitoneal injection studies.*

COMMENT: P81, L31 to P82, L1 and P82, L12-13: The Reviewer suggested that unpublished industry studies summarized in Kier and Kirkland (2013) and others should be summarized in the appropriate genotoxicity tables because they are mentioned in the text.

RESPONSE: *Kier and Kirkland (2013) and other secondary sources are publicly available; however, the unpublished studies are not. Therefore, they are not individually summarized in the toxicological profile.*

COMMENT: P82, L6: The Reviewer suggested identifying the Peluso et al. (1998) study as a follow-up to the Bolognesi (1997) study.

RESPONSE: *These are two separate studies that employed different doses. It does not appear relevant to treat one as a follow-up study.*

COMMENT: P83, L20-23: The Reviewer indicated that the results from the study of Rodrigues et al. (2011) seem anomalous and suspect.

RESPONSE: *The point is acknowledged. However, there appears to be no clear reason to exclude mentioning the results.*

COMMENT: P83, L29-32: The Reviewer stated "The results of Heydens et al. (2008) should be included here. It attempted to repeat the Bolognesi study. It should be noted in the text that considerable toxicity was seen in the liver and kidney at these high ip doses."

RESPONSE: *The results of Heydens et al. (2008) were added, along with a statement that the dose level employed by Bolognesi et al. (1997) elicited marked liver and kidney toxicity (suggesting that the genotoxic effects were secondary to local toxicity).*

COMMENT: P84, L5: The Reviewer stated that results of summarized human studies have significant limitations. The Reviewer suggested possibly indicating that other entities such as JMPR and ECHA reviewed the human data and considered the results to be equivocal.

RESPONSE: *Because the studies in this paragraph were not specifically identified by FAO and WHO (2016) or ECHA (2017), the suggested statement was not added. However, the subsequent paragraph of the toxicological profile indicates that most agencies and other entities have concluded that available data regarding glyphosate do not support a genotoxicity role. EFSA (2016) and ECHA (2017) were added to the list.*

COMMENT: P84, L6: The Reviewer stated "The results of the Koureas et al., 2014 study should be considered for addition."

RESPONSE: *Koureas et al. (2014) reported a significant association between glufosinate ammonium (not glyphosate) and increased 8-OHdG levels (indicator of oxidative DNA damage) in blood samples from pesticide applicators. There was no significant association for glyphosate. Therefore, the results were not included.*

COMMENT: P89, L13: The Reviewer stated "Glyoxylate, an aldehyde and electrophilic metabolite, has recently been identified as a metabolite of glyphosate in mice by Ford et al. (2017). The information from this study should be included in this section."

RESPONSE: *Ford et al. (2017) was reviewed and relevant information was added to the toxicological profile.*

COMMENT: P90, L31-35: The Reviewer stated "The iv portion of this study indicates that almost all of the glyphosate that reaches the blood is excreted in the urine. This implies that most of the glyphosate seen in the feces in the oral experiments is unabsorbed glyphosate. A study briefly mentioned in Gohre et al. (1987) and one described in JMPR (2004) indicate there is little biliary excretion. I recommend that this information be added to the text."

RESPONSE: *The information regarding comparative data on elimination following intravenous, intraperitoneal, and oral exposure of rats was added to this section. A reliable primary source of information regarding biliary excretion was not located; therefore, a statement regarding biliary excretion was not added.*

COMMENT: P94, L9: Regarding the statement a lack of biomarkers of effect specific to glyphosate toxicity, the Reviewer stated "This is true but the chromosomal and DNA damage measured in glyphosate-exposed human populations would be considered by many as a non-specific biomarker of effect."

RESPONSE: *The point was acknowledged. However, a statement was not added due to uncertainty regarding clear evidence of glyphosate-induced genotoxicity in exposed human populations.*

COMMENT: P94, L15-18: The Reviewer suggested adding the following text: "Glyphosate can act as a chelating agent and it has been hypothesized that its interaction with heavy metals in the environment plays a role in the chronic kidney disease that has been seen in pesticide-exposed workers in Sri Lanka and

elsewhere (Jayasumana et al. 2014)." The Reviewer noted that the statement is speculative and may or may not be of value.

RESPONSE: *The suggested addition was not made because it is considered too speculative.*

COMMENT: P94, L21: The Reviewer suggested adding a section 3.5 (Mechanisms of Action) and including information provided by Ford et al. (2017). The Reviewer stated: "Although the study used ip injection at fairly high doses, it identified a reactive metabolite and potential targets that may explain some of glyphosate's toxic effects."

RESPONSE: *ATSDR considers the available mechanistic data to be too speculative given a high level of uncertainty regarding glyphosate toxicity and/or carcinogenicity to mammals. Mode-of-action data for glyphosate carcinogenicity are not presented in this Toxicological Profile for Glyphosate because the carcinogenicity of glyphosate is questionable. Although Ford et al. (2017) provided some indication that high doses of glyphosate (7 days of intraperitoneal injection to mice at 200 mg/kg/day) could result in formation of reactive metabolites in mouse liver, available studies in animals exposed orally for months to a lifetime do not indicate that the liver is a particularly sensitive target of toxicity at doses as high as hundreds to thousands of mg/kg/day.*

COMMENT: P122, Table 5-7: The Reviewer stated that Battaglin et al. (2014) should be re-checked because apparently only 23 states were monitored for glyphosate in groundwater.

RESPONSE: *The source was consulted and it was confirmed that the samples came from only 23 states. The text was revised accordingly.*

COMMENT: P123, Table 5-8: The Reviewer noted that Battaglin et al. (2014) reported soil and sediment detections for glyphosate in Indiana and Mississippi, not 38 states and the District of Columbia.

RESPONSE: *The suggested correction was made.*

COMMENT: P124, L1: The Reviewer stated "Glyphosate levels in a range of crops in different regions of the world can be found in JMPR(2016). You might want to include them here."

RESPONSE: *The statement was slightly revised and cited to FAO and WHO (2016) as well.*

COMMENT: P125, L2: The Reviewer asked whether the statement regarding 3.71 pounds of glyphosate refers to lb/acre.

RESPONSE: *Yes, the correction was made.*

COMMENT: P126, L13-14: Regarding the statement "Human intake of glyphosate via food and water such as total diet studies are not available.", the Reviewer stated: "The FAO and WHO have recently updated their International Estimated Daily Intake values for glyphosate. (see Annex 3 in JMPR 2016). I recommend that these be included. In all cases, the values were 1% or less than the ADI established by the

JMPR. It might also be mentioned that residues might be higher in crops where glyphosate is used shortly before harvest (e.g. sugarcane, Dalley and Richardson, 2010)."

RESPONSE: *The statement regarding the lack of availability of human intake of glyphosate was deleted. The following statement was added: "However, the Joint FAO/WHO Meeting on Pesticide Residues listed International Estimated Daily Intake (IEDI) of glyphosate from 17 GEMS/Food (Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme) cluster diets to range from 140.5–443.0 µg/person (FAO and WHO 2016)."*

COMMENT: P126, L31: The Reviewer asked whether the value of 175 µg of glyphosate in the daily urine should be an amount per volume of urine.

RESPONSE: *It was made clear that the amount (175 µg of glyphosate) did not refer to a concentration (e.g., 175 µg/L urine).*

COMMENT: P127, Table 5-9: The Reviewer stated "The body fluid or tissue in which these were measured should be included in the table.

RESPONSE: *The particular body fluid was already presented in Table 5-9. The tissue entry was revised to identify specific tissues (brain, blood, liver, kidney).*

COMMENT: P129, L5-8: The Reviewer suggested revisions to a statement regarding estimated dermal and inhalation exposure values in a statement by IPCS (1994).

RESPONSE: *The requested changes were made upon consultation of the original source.*

COMMENT: P134, L25-26: Regarding the statement "MRLs based on animal exposure to glyphosate technical would not adequately reflect human exposure to glyphosate formulations", the Reviewer stated "While this is true, I think that having an MRL that is reasonably accurate is better than not having a safe level identified. I think a more valid reason is that ATSDR is working with a limited database. That is the reason given in the text below."

RESPONSE: *Human exposure to GBFs via its use in weed control includes exposure to all substances in GBFs. No MRLs were derived for GBFs due to the wide variation in glyphosate content and surfactants used in various GBFs and the fact that surfactants can contribute to the toxicity of GBFs. However, the general population may also be exposed to glyphosate and/or its breakdown products by ingesting food or water in which glyphosate is detected. Therefore, health effects data from oral exposure to glyphosate technical are considered relevant to potential derivation of oral MRLs for glyphosate. ATSDR is considering whether to derive oral MRLs for glyphosate based on animal data for glyphosate technical; the results of this consideration will be applied to future drafts of the Toxicological Profile for Glyphosate.*

COMMENT: P134, L26-28: Regarding the statement "MRLs for glyphosate formulations would need to be formulation specific due to the wide variation in glyphosate content and surfactants used in various glyphosate formulations and the fact that surfactants contribute to the toxicity of glyphosate formulations",

the Reviewer stated “Since there are hundreds of different formulations, effectively this means that an MRL will never be set - an outcome that does not address the concerns of the public.”

RESPONSE: *There are some data on GBFs, but not sufficient data to derive MRLs. The concentration of glyphosate in GBFs varies. GBFs also contain other additives (e.g., surfactants), and the data indicate that these additives may be more toxic than the active ingredient.*

COMMENT: P137, L19-21: The Reviewer suggested adding the following text: “The National Toxicology Program (NTP 2017) and the Ramazzini Institute in Italy have initiated studies on glyphosate and selected formulation products.” The Reviewer provided references in the General Comments section of the peer-review submissions.

RESPONSE: *A statement was added regarding the NTP ongoing investigation. However, a statement regarding studies initiated at the Ramazzini Institute was not added because available information was located only from news agencies and not from the institute itself or any other reliable scientific source.*

COMMENT: P138, Table 7-1: The Reviewer suggested adding cancer evaluation results for EFSA, JMPR, and ECHA.

RESPONSE: *The suggested additions were not made because this section is intended to present cancer classifications only from HHS, EPA, and IARC. EFSA, JMPR, and ECHA were included in Section 2.19.*

Comments provided by Reviewer #2:

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

General Comments

Comment #1, page 1: The Reviewer stated "This section well address the toxicity data for animals and human being. My criticism is about the segmented range of doses describing LOAELs and NOAELS (detailed in the next chapter): there are several studies performed with hundreds of mg and fewer data for dozens of mg. It seems to force higher LOAELs. The data need presented in the Chapter 6 should include intermediate levels of exposure besides also the analysis of commercial formulations of glyphosate."

RESPONSE: *Available acute-, intermediate-, and chronic-duration oral animal studies have identified NOAEL values >100 mg/kg/day for glyphosate technical. This level is many times greater than expected intake of glyphosate from food or drinking water sources. Therefore, additional acute- or intermediate-duration oral animal studies do not appear necessary. A statement was added to Chapter 6 to indicate a data need for additional animal studies to assess the toxic effects of exposure to a variety of glyphosate formulations.*

Specific Comments

COMMENT: P12, L23-24: The Reviewer stated "The information contained in this section is presented in a descriptive manner, without there being any interpretation of the presented facts, as expected. The statement about "limited use in some aquatic environments" assumes that this use is not particularly important. I suggest that the word "limited" be removed, given that it automatically creates the idea of a comparison: is usage in soil extremely widespread? This section does not discuss this relation on quantity usage. This issue is more properly addressed in chapter 5 Pag 101 line 20."

RESPONSE: *The word "limited" was deleted.*

COMMENT: P13, L11-13: Regarding the statement "no data were located regarding glyphosate concentrations in breast milk", the Reviewer stated "I understand the methodology used to select the articles that are part of this draft, but to assert that there is no data for this parameter is incorrect. I suggest it be added that there are controversies around the subject (Bus 2015, McGuire et al 2016)."

RESPONSE: *The statement in question was replaced with the following: "Glyphosate is not likely to bioaccumulate in breast milk (Bus 2015) and was not detected in breast milk from lactating mothers with detectable glyphosate in their urine (McGuire et al. 2016). The information in the unpublished report of Honeycutt and Rowlands (2014) was not included because the data were judged to be unreliable and were not peer reviewed.*

COMMENT: P16, L12-13: Regarding the incidence of kidney tumors in glyphosate-treated mice, the Reviewer stated "I suggest to include the information: 'the incidence of tumors is not different from historical control.'"

RESPONSE: *The suggested addition was not made. This discussion is clearly presented in Chapter 2.*

COMMENT: P16, L20-22: The Reviewer stated "In the previous paragraph, it is said that there is no evidence of carcinogenicity in animals, but IARC's claim that there is not 'sufficient evidence' of carcinogenic risk in animals seems to fragilize the document. I understand that there are specific procedures to be taken by regulatory agencies, but it is clear that there are divergences in interpreting the results."

RESPONSE: *The statement was revised to clearly note that the lack of evidence of carcinogenicity in the rat studies and the mouse study was a conclusion of EPA (2015c).*

Specific charge questions to the Reviewer

Do you agree with those effects known to occur in humans as reported in the text? The Reviewer agreed.

RESPONSE: *No response is necessary.*

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. The Reviewer stated "Yes. The fact that the effect in human beings is not yet proven does not exclude its existence. The experimental conditions in lab animals are completely controlled and the correlation between cause and effect can be easily stipulated. The human being, however, is exposed to a great variety of factors that can interfere in the correlations between cause and effects, not meaning however that the suspect parameters should not be monitored due to that difficulty."

RESPONSE: *No response is necessary.*

Have exposure conditions been adequately described? If you disagree, please explain. The Reviewer agreed.

RESPONSE: *No response is necessary.*

If MRLs have been derived, are the values justifiable? If no MRLs have been derived, do you agree that the data do not support such a derivation? The Reviewer stated "Only one study has been derived for intermediate exposure and only one more for chronic exposure to technical glyphosate. In no study performed with glyphosate formulations it was possible to establish the derivative. If the human being is exposed to the formulations of glyphosate and not the technical glyphosate, and the derivation to the formulations can't be precised, it may be more recommended to not use such parameters. The reader can be lead to believe that such dose is not deleterious, but he does not have the conditions to interpret that it does not correspond to the product he is in fact exposed to (commercial formulation), which likely has a higher level of toxicity."

RESPONSE: *ATSDR did not derive MRLs for glyphosate technical. The depiction of MRLs in the LSE figure was in error. This depiction was removed.*

CHAPTER 2. HEALTH EFFECTS

General comments

Comment #1, page 3: The Reviewer stated "This section is very clear. The tables and graphics are quite informative. I have some specific comments above addressed."

RESPONSE: *See responses to Specific Comments in Reviewer comments on Chapter 1 above.*

Specific questions

2.1 - Toxicity - Quality of Human Studies

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. The Reviewer stated "Yes, these issues were adequately addressed."

RESPONSE: *No response is necessary.*

Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the profile? The Reviewer stated "Yes, the conclusions drawn were appropriate and accurately reflected in the profile."

RESPONSE: *No response is necessary.*

Were the appropriate statistical tests used in the studies? Would other statistical tests have been more appropriate? Were statistical test results of study data evaluated properly? NOTE: As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data. The Reviewer stated "I agree with the statistical tests used. Additionally, these studies were previously peer reviewed by respective journals."

RESPONSE: *No response is necessary.*

Are you aware of other studies which may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included. The Reviewer stated "I agree with the procedures detailed in the "Literature review framework", presented in appendix B."

RESPONSE: *No response is necessary.*

2.2 - Health Effects in Humans Exposed Tables

Are the study details and author conclusions presented accurately? The Reviewer stated "Yes, the study details and author conclusions are presented accurately. The evaluation of prospective studies in human

populations from different American States is very pertinent for the evaluation of the product's safety. The chart was clear, with emphasis in the most important points and of easy interpretation. I suggest adding a hyperlink in terms taken from Appendix 6, such as OR, for example."

RESPONSE: *ATSDR will consider adding a hyperlink to acronyms defined in an appendix for future drafts of toxicological profiles.*

2.3 - Toxicity - Quality of Animal Studies

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? The Reviewer stated "In the Page 25 Table 2.1: In the study presented in the figure key 3, the range between LOAEL (1,000) and NOAEL (3,500) is too large. What could happen in the doses between 1,000 and 3,500? In the Page 26 Table 2.1 cont.: The range of doses presented in the figure key 7 are very much lower than the others used in the study. There is a large discrepancy between the doses in these selected studies. I believe that an intermediate range of doses could better address the LOAELs and NOAELs, but I do not consider these selected studies to be inadequate."

RESPONSE: *Available acute-, intermediate-, and chronic-duration oral animal studies have identified NOAEL values >100 mg/kg/day for glyphosate technical. This level is many times greater than expected intake of glyphosate from food or drinking water sources. Therefore, additional acute- or intermediate-duration oral animal studies do not appear necessary. A statement was added to Chapter 6 to indicate a data need for additional animal studies to assess the toxic effects of exposure to a variety of glyphosate formulations.*

Were the animal species appropriate for the most significant toxicological endpoint of the study? The Reviewer stated "Yes, and it is possible to note the differences in toxicity among the species."

RESPONSE: *No response is necessary.*

Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the text? The Reviewer stated "Yes, the conclusions drawn by the authors of the studies are appropriate and accurately reflected in the text."

RESPONSE: *No response is necessary.*

Were all appropriate NOAELs and LOAELs identified for each study? Were all appropriate toxicological effects identified for the studies? If not, please explain. The Reviewer stated "I commented on this issue previously.

RESPONSE: *See previous response.*

If appropriate, is there a discussion of the toxicities of the various forms of the substance? The Reviewer stated "Yes, there is.

RESPONSE: *No response is necessary.*

Were the appropriate statistical tests used in the interpretation of the studies? If not, which statistical tests would have been more appropriate? Were statistical test results of study data evaluated properly? NOTE: As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data. The Reviewer stated "I agree with the statistical tests used. Additionally, these studies were previously peer reviewed by respective journals.

RESPONSE: *No response is necessary.*

Are you aware of other studies that may be important in evaluating the toxicity of the substance? If you are citing a new reference, please provide a copy and indicate where (in the text) it should be included. The Reviewer stated "I agree with the procedures detailed in the "Literature review framework", presented in appendix B.

RESPONSE: *No response is necessary.*

2.4 - Levels of Significant Exposure (LSE) Tables and Figures

Are the LSE tables and figures complete and self-explanatory? Does the "Users Guide" explain clearly how to use them? Are exposure levels (units, dose) accurately presented for the route of exposure? Please offer suggestions to improve the effectiveness of the LSE tables and figures and the "User's Guide." The Reviewer stated "Yes, but in the pages 32 and 34 Fig 2.3 it is not clear what the dotted line is indicating. In the page 25 Table 2.1: In the figure key 2 "mixed" could be switched for the number of males and females used in the study, as for the other studies.

RESPONSE: *The term "mixed" was used because the number of males/females per dose group varied (i.e., one group included two males and three females, whereas another group included three males and two females).*

Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? The Reviewer stated "No. Based on that interpretation, alterations such as reproductive ones are not particularly important. However, how would a species perpetuate if it had difficulties reproducing? Would that not be an important consequence? Specifically, in the page 25 Table 2.1 'depressed mean fetal body and increased incidence of unossified sternebrae' are considered less serious."

RESPONSE: *ATSDR categorizes depressed body weight or body weight gain of 10–20% as "less serious" and >20% as "serious". Guidance document available at: https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf.*

2.5 - Evaluation of Text

Have the major limitations of the studies been adequately and accurately discussed? How might discussions be changed to improve or more accurately reflect the proper interpretation of the studies? The Reviewer stated "Yes, but I do not consider the use of commercial formulation a limitation of the study, since this is the product available for consumers."

RESPONSE: *No response is necessary.*

Has the effect, or key endpoint, been critically evaluated for its relevance in both humans and animals? The Reviewer stated "Yes, the effect/key endpoint has been critically evaluated for its relevance in both humans and animals."

RESPONSE: *No response is necessary.*

Have "bottom-line" statements been made regarding the relevance of the endpoint for human health? The Reviewer stated "Yes, "bottom-line" statements have been made regarding the relevance of the endpoint for human health."

RESPONSE: *No response is necessary.*

Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text. The Reviewer stated "The draft describes the toxicity data for glyphosate, technical and formulations. Only the results for technical glyphosate seem to be discussed in a more reliable way. I disagree with this approach because the human being is exposed to commercial formulations, not only for glyphosate salt. The inert ingredients are fundamental for the herbicide performance in the crops and are not dissociated from glyphosate salt. In this manner, animal studies conducted with commercial formulation could provide more accurate data to compare with glyphosate human exposure."

RESPONSE: *ATSDR is aware that human exposure is most likely to occur with commercial formulations. Publicly available information regarding health effects in laboratory animals exposed to commercial formulations is presented in the toxicological profile in the most reliable manner possible from the available database.*

Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain. The Reviewer stated "Yes, the levels of exposure are clear in the text."

RESPONSE: *No response is necessary.*

Has the animal data been used to draw support for any known human effects? If so, critique the validity of the support. The Reviewer stated "Yes, especially in the carcinogenic studies. It is necessary to emphasize that the human being is exposed to commercial formulation of glyphosate while all studies performed by regulatory agencies used technical glyphosate. This is a confusion factor, because the inert ingredients, such as POEA, may have significant toxicity and yet they are not evaluated."

RESPONSE: *The following statement was added to Section 2.1 of the toxicological profile where glyphosate technical and glyphosate formulations are addressed: "The general population is most likely to be exposed to glyphosate formulations, not glyphosate technical. As such, health effects observed in studies of animals exposed to relatively high levels of glyphosate technical may not reflect health effects from exposure to glyphosate formulations."*

2.6 - Mechanisms of Action

Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. The Reviewer stated "No, because there are several others studies developed not only in animal models, but also in cells in culture, that examine the mechanisms of action in depth. The objective of this draft is to be informative and I believe that the readers interested in these mechanistic studies may search in the literature."

RESPONSE: *A Mechanisms of Action section (Section 2.21) was added to the profile.*

2.7 - Hazard Identification/Systematic Review Information

Are the hazard identifications clear and justifiable based on ATSDR's SR process? The Reviewer stated "Yes, the hazard identifications are clear and justifiable based on ATSDR's SR process."

RESPONSE: *No response is necessary.*

Do you agree with the selection of endpoints that was carried forward through the SR process? The Reviewer stated "Yes, I agree with the selection of endpoints that was carried forward through the SR process."

RESPONSE: *No response is necessary.*

Do you agree with the SR framework as presented in Appendix B? Are there any steps that need to be revised? The Reviewer stated "Yes, I agree with the SR framework as presented in Appendix B. No, there are no steps that need to be revised."

RESPONSE: *No response is necessary.*

Section 3.1 TOXICOKINETICS

Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? The Reviewer stated "Yes, this issue is adequately addressed."

RESPONSE: *No response is necessary.*

Have the major organs, tissues, etc. in which the substance is stored been identified? If not, suggest ways to improve the text. The Reviewer stated "No, since the substance is not stored in major organs, tissues or anything of the sort."

RESPONSE: *No response is necessary.*

Have all applicable metabolic parameters been presented? Have all available pharmacokinetic/ pharmacodynamic models and supporting data been presented? If not, please explain. The Reviewer stated "Yes, all applicable metabolic parameters have been presented. Yes, all available pharmacokinetic/ pharmacodynamics models and supporting data have been presented."

RESPONSE: *No response is necessary.*

Is there adequate discussion of the differences in toxicokinetics between humans and animals? What other observations should be made? The Reviewer stated "Yes, but fewer data is available for human toxicokinetics."

RESPONSE: *No response is necessary.*

Is there an adequate discussion of the relevance of animal toxicokinetic information for humans? If not, please explain. The Reviewer stated "Yes, there is an adequate discussion of the relevance of animal toxicokinetic information for humans."

RESPONSE: *No response is necessary.*

If applicable, is there a discussion of the toxicokinetics of different forms of the substance (e.g., inorganic vs. organic mercury)? The Reviewer stated "Yes, the discussion includes data for AMPA, despite less than 1% of glyphosate being metabolized in mammals."

RESPONSE: *No response is necessary.*

Section 3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? The Reviewer stated "This information is very limited in the literature."

RESPONSE: *No response is necessary.*

Are there valid tests to measure the biomarker of exposure? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist. The Reviewer stated "No, there are no valid tests to measure the biomarker of exposure. Yes, this is consistent with statements made in other sections of the text."

RESPONSE: *No response is necessary.*

Are the biomarkers of effect specific for the substance or are they for a class of substances? If they are not specific, how would you change the text? The Reviewer stated "No, there are no specific biomarkers of effect for glyphosate. I would not change the text."

RESPONSE: *No response is necessary.*

Are there valid tests to measure the biomarker of effect? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist. The Reviewer stated "No, there are no valid tests to measure the biomarker of effect. Yes, this is consistent with statements made in other sections of the text."

RESPONSE: *No response is necessary.*

Section 3.4 INTERACTIONS WITH OTHER CHEMICALS

Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? If not, please clarify and add additional references. The Reviewer stated "The literature strongly suggests an association between glyphosate and surfactants, but very few studies used these components separately. Therefore, additional studies are necessary."

RESPONSE: *The following statement was added to Chapter 6: "Additional animal studies should be designed to assess the toxic effects of exposure to a variety of glyphosate formulations and individual components suspected to be toxic."*

If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? If not, please clarify and provide any appropriate references. The Reviewer stated "No, the mechanisms of these interactions are not discussed. Additional studies are necessary to better understand these interactions."

RESPONSE: *The following statement was added to Chapter 6: "Additional animal studies should be designed to assess the toxic effects of exposure to a variety of glyphosate formulations and individual components suspected to be toxic. Such studies could also be designed to evaluate possible interactions among individual components that might enhance toxicity."*

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

Are you aware of any information or values that are wrong or missing in the chemical and physical properties tables? Please provide appropriate references for your additions or changes. The Reviewer stated "No, I am not aware of any information or values that are wrong or missing in the chemical and physical properties tables."

RESPONSE: *No response is necessary.*

Is information provided on the various forms of the substance? If not, please explain. The Reviewer stated "Yes, information is provided on the various forms of the substance."

RESPONSE: *No response is necessary.*

Section 5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Are you aware of any information that is wrong or missing? If so, please provide copies of the references and indicate where (in the text) the references should be included. The Reviewer stated "No, I am not aware of any information that is wrong or missing and I believe that the relevant studies are present."

RESPONSE: *No response is necessary.*

Sections 5.3-5.7

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. The Reviewer stated "Yes, the text has appropriately traced the substance from its point of release to the environment until it reaches the receptor population. Yes, the text provides sufficient and technically sound information regarding the extent of occurrence at NPL sites. No, I do not know of any other relevant information."

RESPONSE: *No response is necessary.*

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. The Reviewer stated "Yes, the text covers pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media. No, I do not know of any other relevant information."

RESPONSE: *No response is necessary.*

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. The Reviewer stated "Yes, the text provides information on levels monitored or estimated in the environment, including background levels. Yes, proper units are used for each medium. Yes, the information includes the form of the substance measured. Yes, there is an adequate discussion of the quality of the information. No, I do not know of any other relevant information."

RESPONSE: *No response is necessary.*

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? The Reviewer stated "Yes, the text describes 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. Yes, I agree with the selection of these populations."

RESPONSE: *No response is necessary.*

Section 6.1 INFORMATION ON HEALTH EFFECTS

Do you know of other studies that may fill a data gap? If so, please provide the reference. The Reviewer stated "No, I do not know of any other studies that may fill a data gap."

RESPONSE: *No response is necessary.*

Section 6.2 IDENTIFICATION OF DATA NEEDS

Are the data needs presented in a neutral, non-judgmental fashion? Please note where the text shows bias. The Reviewer stated "Yes, the data is presented in a neutral, non-judgmental fashion."

RESPONSE: *No response is necessary.*

Do you agree with the identified data needs? If not, please explain your response and support your conclusions with appropriate references. The Reviewer stated "Yes, I agree with the identified data needs. More studies are necessary to better address the toxicity of glyphosate."

RESPONSE: *No response is necessary.*

Does the text indicate whether any information on the data need(s) exist(s)? The Reviewer stated "Yes, the text indicates that information on the data needs exists."

RESPONSE: *No response is necessary.*

Does the text adequately justify why further development of the data need(s) would be desirable; or, conversely, justify the "inappropriateness" of developing the data need(s) at present? If not, how can this justification be improved. The Reviewer stated "Yes, the data need is justified and the important "inappropriateness" is highlighted. For example, in the page 133 lines 25-28: "MRLs based on animal exposure to glyphosate technical would not adequately reflect human exposure to glyphosate formulations. MRLs for glyphosate formulations would need to be formulation specific due to the wide variation in glyphosate content and surfactants used in various glyphosate formulations and the fact that surfactants contribute to the toxicity of glyphosate formulations."

RESPONSE: *No response is necessary.*

CHAPTER 7. REGULATIONS AND GUIDELINES

Are you aware of other regulations or guidelines that may be appropriate for the table? If so, please provide a copy of the reference. The Reviewer stated "No, the regulation and guidelines are appropriate as it is."

RESPONSE: *No response is necessary.*

CHAPTER 8. REFERENCES

Are there additional references that provide new data or are there better studies than those already in the text? If so, please provide a copy of each additional reference. The Reviewer stated "Yes, there are two references to be evaluated for inclusion in the text.

Bus, J. S. (2015). Analysis of Moms Across America report suggesting bioaccumulation of glyphosate in US mother's breast milk: Implausibility based on inconsistency with available body of glyphosate animal toxicokinetic, human biomonitoring, and physico-chemical data. Regulatory Toxicology and Pharmacology, 73(3), 758-764.

McGuire, M. K., McGuire, M. A., Price, W. J., Shafii, B., Carrothers, J. M., Lackey, K. A., Vicini, J. L. (2016). Glyphosate and aminomethylphosphonic acid are not detectable in human milk. The American journal of clinical nutrition, 103(5), 1285-1290."

RESPONSE: *The identified studies were retrieved and relevant information was added to the toxicological profile.*

Reviewer #2 peer-reviewed the following 4 unpublished sources for information in the Toxicological Profile for Glyphosate and provided comments on each source:

Agrisolutions. 2010. The Reviewer stated "It is an official document for pesticide registration (62% glyphosate IPA) by Winfield Solutions in the US Environmental Protection Agency, process number 1381-245. In the first two pages, the US EPA enumerates six changes to the label necessary to pesticide approval. In the following pages (3-8) label information and safety instructions are detailed. This version of the document do not include these necessary changes in the label. I suggest that the final document revised by manufacturer is the one to be cited in this Toxicological Profile."

RESPONSE: *Agrisolutions (2010) is considered the appropriate reference for the information contained in the toxicological profile.*

Alferness PL. 1994
The Reviewer stated "It is a study performed by Zeneca Ag Products for the evaluation of gas chromatograph and mass-selective detection methods for the identification of glyphosate and AMPA in crops. All experiments data are present in the text. The study is adequate."

RESPONSE: *No response is necessary.*

EPA. Undated.
It is a data evaluation record of glyphosate acid performed by Zeneca Inc. This document briefly describes the degradation of glyphosate in three different pH conditions. The data is partially presented. Additional information, if necessary, should be request as suggested at the bottom of the page 5. The document is sufficient for a general understand of what was evaluated by the company for the parameters of glyphosate acid degradation.

RESPONSE: *No response is necessary.*

Pioneer. 2006.
It is an Early Food Safety Evaluation for a Glyphosate N-Acetytransferase Protein: GAT4601 presented by Pioneer. The purposes of include GAT4601 protein in the transgenic crops resistant to glyphosate are clear. The evaluation of GAT4601 protein includes its production, behavior in the gastrointestinal simulated environments, the glycosylation status (allergenic potential) and toxicity studies in mice. There are no toxicity reported for mice. The document is adequate for to be cited in this Toxicological Profile.

RESPONSE: *No response is necessary.*

Comments provided by Reviewer #3:

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

General comments

ATSDR outlined the purpose of Chapter 1 as follows: *"The purpose of this section is to evaluate and interpret the significance of existing toxicity data and, in some cases, speculate regarding the significance of this information as it relates to human health. Specifically, the text should address: effects known to occur in humans; effects observed in animals but not in humans; and exposure conditions (route, duration, or level) that are likely to be of concern to humans, especially around hazardous waste sites."*

The Reviewer stated "The information in this section is presented as a summary of the findings, rather than an evaluation and interpretation of the significance of existing toxicity data (as described above). It is difficult to know what the conclusions are exactly, except that these associations were observed in various studies. It would actually be very helpful if the text were organized with clear headings for the main points to be addressed: effects known to occur in humans; effects observed in animals but not in humans; and exposure conditions (route, duration, or level) that are likely to be of concern to humans.

In section 1.2, Summary of Health Effects, the only effects listed are those resulting from glyphosate technical in animals. It is a serious omission not to include the findings for glyphosate formulations. If these findings are not considered relevant or informative for public health, then why were these studies reviewed at all? It has been acknowledged that there may be interaction between glyphosate and surfactants, or part of the effect may be due to surfactants, but these data are important because they suggest effects occurring at lower dose levels than for glyphosate technical alone."

RESPONSE: *The following text was added to Section 1.2:*

"Collectively, animal studies in which glyphosate-containing herbicide formulations were tested by the oral exposure route have identified the following targets of toxicity:

- *Body weight effects (**d**epressed body weight gain in mice),*
- *Hematological effects (decreases in red blood cells, hematocrit, and hemoglobin, and increases in mean corpuscular volume and neutrophils in mice),*
- *Hepatic effects (increased serum liver enzyme activity and histopathologic liver lesions in male rats),*
- *Renal effects (histopathologic kidney lesions in male rats), and*
- *Reproductive effects (increased percentage of morphologically abnormal sperm in rats).*

A summary figure of sensitive targets of glyphosate-containing herbicide formulations is not included in this toxicological profile for glyphosate because formulations were not equivalent across studies and other ingredients (in addition to glyphosate as active ingredient) may have influenced the observed effects."

Reviewer comments on ATSDR charge questions

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. The Reviewer stated "There were no effects known to occur in human reported in the text. Section 1.2 only includes health effects found in animals from glyphosate technical."

RESPONSE: *Section 1.2 does mention human studies that evaluated carcinogenicity. Chapter 3 provides detailed discussion of studies that reported on possible associations between exposure to glyphosate and selected health outcomes.*

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. The Reviewer stated "Yes, the effects observed in animals are likely to also be of concern for humans, due to the similarity of organ systems between mammals. However, the significance of the information from the animal studies for human health is not discussed in the document."

RESPONSE: *The following statement was added to Section 1.2: "Effects observed in animals are considered relevant to human health in the absence of experimental data to indicate otherwise."*

Have exposure conditions been adequately described? If you disagree, please explain. The Reviewer stated "Exposure conditions have for the most part been adequately described; however, provide some indication that glyphosate residues have been detected in many different types of food products; therefore, a total diet study needs to be done to characterize typical exposures."

RESPONSE: *A statement was added to Section 5.6 to note glyphosate residue intake from a variety of food sources. Chapter 6 (Exposure Levels in Humans) states "Studies are needed to investigate human intake of glyphosate via food and water, such as total diet studies."*

If MRLs have been derived, are the values justifiable? If no MRLs have been derived, do you agree that the data do not support such a derivation? The Reviewer stated "No MRL was derived. I disagree with the reasons for not deriving an MRL as part of this review, and I find the explanation of why MRLs were not derived to be a circular argument that is in some ways contradictory. According to this argument, the health effects of glyphosate technical are considered the most relevant/the strongest data, but in contradiction, humans aren't exposed to glyphosate technical so MRLs were not derived since they would not 'adequately reflect' risk from glyphosate formulations. On the other hand, the data from glyphosate formulations were not included in the main health effects conclusions because some of the effects may be due to surfactants rather than glyphosate. Even though this is considered the more relevant ('real life') exposure, MRLs were not derived for glyphosate formulations 'due to the wide variation in glyphosate content and surfactants….'. If we can't (or won't) derive an MRLs for a pesticide that is widely and increasingly distributed in the environment, just because it is typically mixed with other chemicals, then what is the point of conducting this type of review at all?

I believe these conclusions and non-derivation of an MRL detract from the utility of this document for the public health and medical community. With greater effort, MRLs could be derived from the studies based on glyphosate formulations, using information about known glyphosate content in the formulations used for dosing in these studies. While it is true that part of the effect may be from surfactant, the MRL is defined as "an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure." It is not defined as an accurate dose relating to an effect. In many cases, such MRLs or other types of thresholds are known to be conservative (health protective), as it would likely be in this instance with the MRL based on glyphosate formulation data."

RESPONSE: *There is some information on GBFs, but it is not sufficient to derive MRLs. The concentration of glyphosate in GBFs varies. GBFs also contain other additives (e.g., surfactants), and the data indicate that these additives may be more toxic than the active ingredient. In addition, much of the information on the GBFs is proprietary.*

Human exposure to GBFs via its use in weed control includes exposure to all substances in GBFs. No MRLs were derived for GBFs due to the wide variation in glyphosate content and surfactants used in various GBFs and the fact that surfactants can contribute to the toxicity of GBFs. However, the general population may also be exposed to glyphosate and/or its breakdown products by ingesting food or water in which glyphosate is detected. Therefore, health effects data from oral exposure to glyphosate technical are considered relevant to potential derivation of oral MRLs for glyphosate. ATSDR is considering whether to derive oral MRLs for glyphosate based on animal data for glyphosate technical; the results of this consideration will be applied to future drafts of the Toxicological Profile for Glyphosate.

CHAPTER 2. HEALTH EFFECTS

General Comments

The Reviewer stated "The chapter should include an explanation up front of the criteria used to denote an 'association' or 'effect' in this ATSDR review. I glean that 'associations' are designated as such based on statistical significance, defined with a p-value cutoff of <0.05, but this should be explicitly stated.

One broad comment: I find the extensive detailing of the conclusions and opinions from the EPA OPP 2016 document to be disturbing. This ATSDR review of the cancer studies appears to rely heavily on the conclusions from EPA OPP. I have not read the EPA OPP document, but as described here, it relies heavily on use of historical controls in order to dismiss most of the carcinogenicity assays. Other carcinogenicity assays are dismissed based on issues of multiple comparisons or the fact that precancerous lesions were not observed. These EPA OPP conclusions are entirely based on the opinions of the review committee that conducted that review, and in some instances I disagree with their approach, as presented here. Regardless, I understood that this ATSDR Toxicological Profile was to be an independent systematic review of the literature, based on the SR protocol that was followed. Was that not the pre-defined approach? I was looking for ATSDR's conclusions about the cancer literature, not the EPA's conclusions. Given this, I find it inappropriate to describe and discuss the detailed opinions and conclusions from the EPA OPP here."

RESPONSE: *Most of EPA conclusions were deleted from the toxicological profile. ATSDR does not draw conclusions regarding carcinogenicity, but rather relies on well-established agencies and organizations for such conclusions.*

Reviewer comments on ATSDR charge questions

<u>Toxicity - Quality of Human Studies</u>

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.

The Reviewer stated "Human (epidemiologic) studies identified in the text appear to be adequately designed. The studies were mostly (1) cohort and case-control studies of people who had used glyphosate in their jobs. The major deficiency in these studies, noted in the text, is that the studies mostly estimated risk with ever (vs. never) used glyphosate herbicides, rather than with a quantitative or semi-quantitative exposure measure (like amount, frequency, or duration of use). The text should be more specific regarding what was the exposure metric used in the studies. In many cases, the document says 'any glyphosate exposure', when the actual exposure metric was any glyphosate use'. This is important because it implies the route(s) and level of exposure (as opposed to exposure from the diet, for example).

One study limitation which I believe is inadequately described in the text is adjustment for other pesticides. In reading the literature over the years, I recall that many studies adjust for at least a few other pesticides when evaluating glyphosate. These adjustments sometimes do not end up in the final model, if the adjustment does not substantially affect the glyphosate result. The text points out lack of adjustment as a limitation, which is true; however, it would be warranted to provide more information on a study-by-study basis as to whether any pesticide adjustments were applied, whether or not they are included in the final model.

In general, other major study limitations appear to be sufficiently described in the text; however, please note that I cannot respond to this point with certainty without conducting a review of all the studies myself, and that is beyond the scope of work for this peer review of the ATSDR Toxicological Profile. One limitation that I believe is inadequately described in the text."

RESPONSE: *This section was extensively revised and includes exposure metrics for each individual study summarized in this toxicological profile as well as adjustments for exposure to other pesticides.*

Question: Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the profile? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)? Please suggest appropriate changes.

The Reviewer stated "As a reviewer of this ATSDR Toxicological Profile document, I cannot know if the conclusions drawn by the authors of the studies were appropriate and accurately reflected in the profile, without conducting a review of all the studies myself, which is beyond the scope of work for this peer review of the ATSDR Toxicological Profile."

RESPONSE: *No response is necessary.*

Question: Were all appropriate NOAELs and/or LOAELs identified for each study? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

The Reviewer stated "As a reviewer of this ATSDR Toxicological Profile document, I cannot know if all appropriate NOAELs and/or LOAELs were identified for each study, without conducting a review of all the studies myself, which is beyond the scope of work for this peer review of the ATSDR Toxicological Profile."

RESPONSE: *No response is necessary.*

Question: Are you aware of other studies which may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included**.**

The Reviewer stated "There are at least a couple of studies that have been published since the literature search and selection was completed in 2015. One example is Parks et al. 2016 Environ Health Perspect 124 (a study on rheumatoid arthritis). It seems that the literature search should have been supplemented with new research, as it became available, considering that this is likely to be a limited set of studies."

RESPONSE: *A summary of Parks et al. (2016) was added to the toxicological profile. An updated literature search was conducted for human cancer data and new literature was added to the profile. A more general literature search will be conducted after the public comment period, before releasing the final document.*

Health Effects in Humans Exposed Tables

Question: Are the study details and author conclusions presented accurately?

The Reviewer stated "As a reviewer of this ATSDR Toxicological Profile document, I cannot know the study details and author conclusions are presented accurately, without conducting a review of all the studies myself, which is beyond the scope of work for this peer review of the ATSDR Toxicological Profile."

RESPONSE: *No response is necessary.*

Toxicity - Quality of Animal Studies

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.

The Reviewer stated "The studies identified in the text appear adequately designed. As noted in the text, one of the carcinogenicity studies used an exceptionally high dose that is not typically seen in carcinogenicity studies."

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?

The Reviewer stated "I do not have sufficient expertise to answer this question."

RESPONSE: *No response is necessary.*

Question: Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the text? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)?

The Reviewer stated "As a reviewer of this ATSDR Toxicological Profile document, I cannot know if the conclusions drawn by the authors of the studies were appropriate and accurately reflected in the profile, without conducting a review of all the studies myself, which is beyond the scope of work for this peer review of the ATSDR Toxicological Profile. In some instances where the ATSDR document describes the authors' conclusions, I have made specific comments."

RESPONSE: *See responses to specific comments in the Annotated Pages section following the General Comments from Reviewer #3.*

Question: Were all appropriate NOAELs and LOAELs identified for each study? Were all appropriate toxicological effects identified for the studies? If not, please explain.

The Reviewer stated "As a reviewer of this ATSDR Toxicological Profile document, I cannot know if all appropriate NOAELs and/or LOAELs were identified for each study, without conducting a review of all the studies myself, which is beyond the scope of work for this peer review of the ATSDR Toxicological Profile."

RESPONSE: *No response is necessary.*

Question: If appropriate, is there a discussion of the toxicities of the various forms of the substance? If not, please give examples of toxicological effects that might be important for forms of the substance."

The Reviewer stated "Yes there is a brief discussion of the toxicities of the various forms of the substance, which refers to a few studies that found toxicity associated with surfactants used in glyphosate formulations, that was independent of any glyphosate effects. There is no discussion of toxicities associated with glyphosate vs. AMPA, because this was not tested in any of the animal studies."

RESPONSE: *No response is necessary.*

Question: Were the appropriate statistical tests used in the interpretation of the studies? If not, which statistical tests would have been more appropriate? Were statistical test results of study data evaluated properly? NOTE: As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data.

The Reviewer stated "As a reviewer of this ATSDR Toxicological Profile document, I cannot know if appropriate statistical tests were used in the interpretation of the studies, without conducting a review of all the studies myself – which is beyond the scope of work for this peer review of the ATSDR Toxicological Profile. Nevertheless, comparison of dosing groups to controls by statistical comparisons of incidence appear sound, where presented. What is lacking is any statistical testing of dose-response, such as regression analyses of tests of trend; however, it is unclear whether this was not performed in the original study or was simply not reported in the text of the ATSDR document."

RESPONSE: *ATSDR has included results from statistical tests, particularly from pairwise comparisons between control groups and treated groups when such data were available in source documents.*

Question: Are you aware of other studies that may be important in evaluating the toxicity of the substance? If you are citing a new reference, please provide a copy and indicate where (in the text) it should be included.

The Reviewer stated "There are a couple of studies included in IARC's monograph on glyphosate, which are not included here. It is unclear why, as these studies appear to be available. These studies both applied glyphosate dermally.
-Seralini et al. 2014 Environmental Sciences Europe 26
-George et al. 2010 J Proteomics 73"

RESPONSE: *The study of Seralini et al. (2014) is not included in the toxicological profile because it is the re-publication of the Seralini et al. (2012) study that was retracted in 2013. The results from George et al. (2010) were added to the cancer section.*

Levels of Significant Exposure (LSE) Tables and Figures

Question: Are the LSE tables and figures complete and self-explanatory? Does the "Users Guide" explain clearly how to use them? Are exposure levels (units, dose) accurately presented for the route of exposure? Please offer suggestions to improve the effectiveness of the LSE tables and figures and the "User's Guide."

The Reviewer stated "In general, I find the tables and figures in this section to be excellent – packed full of information in a creative, readily understandable format. The LSE tables and figures are self-explanatory, from the headings and footnotes. In addition, the "Users Guide" explains clearly how to use them. One point which is not clear is the presentation of the MRL in Figure 2-3. Where does this MRL come from, since my understanding is that no MRL was defined based on this review. Is there a previous MRL? Is this the RfD from EPA? If so, it should be labeled as such.

There is no way for me to know whether the LSE tables and figures are complete without having conducting a review of all the studies myself, which is beyond the scope of work for this peer review of the ATSDR Toxicological Profile."

RESPONSE: *The depiction of MRLs in the LSE figure is in error. This depiction has been removed.*

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

The Reviewer stated "In the tables of animal effects, body weight effects are sometimes listed as "serious' and for other findings as "less serious"; the reason for these different categorizations is not clear. In general, I disagree with the categorization of body weight effects as "less serious", as body weight influences every aspect of health and vigor. These effects should be categorized as "serious" in every instance.

Sometimes diarrhea effects are listed as "serious", in other results as "less serious". I agree with the "less serious" categorization."

RESPONSE: *ATSDR categorizes depressed body weight or body weight gain of 10–20% as "less serious" and >20% as "serious". Guidance document available at: https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf.*

Evaluation of Text

Question: Have the major limitations of the studies been adequately and accurately discussed? How might discussions be changed to improve or more accurately reflect the proper interpretation of the studies?

The Reviewer stated "As a reviewer of this ATSDR Toxicological Profile document, I cannot know if the major limitations of the studies have been adequately and accurately discussed, without conducting a review of all the studies myself, which is beyond the scope of work for this peer review of the ATSDR Toxicological Profile. Limitations were certainly described and discussed in the ATSDR document. In most instances, these discussions appear adequate and accurate."

RESPONSE: *No response is necessary.*

Question: Has the effect, or key endpoint, been critically evaluated for its relevance in both humans and animals?

The Reviewer stated "I'm not sure I understand the point of this question – the relevance of the endpoint in what respect? Nevertheless, relevance of the endpoints were not discussed adequately, if at all."

RESPONSE: *The following statement was added to Section 1.2: "Effects observed in animals are considered relevant to human health in the absence of experimental data to indicate otherwise."*

Question: Have "bottom-line" statements been made regarding the relevance of the endpoint for human health?"

The Reviewer stated "I did not see any such 'bottom-line' statements regarding the relevance of the endpoints for human health. In some cases, this makes it difficult to know why an endpoint is categorized as 'less serious' or 'serious'."

RESPONSE: *As stated previously, a statement was added to Section 1.2 to note that effects observed in animals are considered relevant to human health.*

Question: Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.

The Reviewer stated "It is unclear where the main conclusions are presented in Chapter 2. The chapter begins with a summary of effects in animal studies of glyphosate technical and glyphosate-based formulations; however, I do not see an overall summary of effects from the human data. The conclusion for glyphosate technical effects of cancer is: "Glyphosate is presently being re-evaluated for potential to cause cancer". This seems inappropriate, as the other conclusions are based on the currently available data.

In general, the grouping of some of the effects by endpoint could have been done differently, and if so, may have led to different conclusions. For example:

1.Romano et al. 2010 saw decreased serum testosterone and decreased epithelial thickness and increased luminal diameter in seminiferous tubules w/ glyphosate formulation of 5 mg/kg/day, which were grouped as endocrine and developmental endpoints. Dallegrave et al. 2007 found decreased sperm production and histopathologic testicular lesions at 50 mg/kg/day, which were grouped as developmental effects, and Cassault-Meyer et al. 2014 observed up to 18% increased percent abnormal sperm morphology at 640 mg/kg/day, which was classified as a reproductive effect. Since these various results are discussed in different sections. However, when considered together they suggest an effect to male reproductive success. All of these effects are seen at relatively low doses, and should be reconsidered for commonality of effect.

2. Renal tubule dilation in offspring is listed as a developmental effect rather than a renal effect. This may be appropriate, but it caught my eye as something that could be rightly considered a renal effect.

3. ADD/ADHD and spontaneous abortion/miscarriages&preterm delivery are listed under developmental effects instead of neurological or reproductive, respectively. Preterm delivery is not typically considered as a developmental effect, and the others are debatable."

RESPONSE: *The statement "Glyphosate is presently being re-evaluated for potential to cause cancer" was replaced with the following: "Upon evaluation of available carcinogenicity studies in laboratory rodents, a number of agencies or organizations have concluded that glyphosate technical does not appear to be an animal carcinogen. In contrast, IARC considered the animal data to provide 'sufficient evidence' of glyphosate carcinogenicity."*

ATSDR typically defines effects occurring postimplantation as developmental effects. Therefore, information regarding miscarriage is presented in the developmental toxicity section. The animal studies in question were performed using maternal exposure during gestation/lactation; therefore, the results in offspring are considered developmental.

Question: Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

The Reviewer stated "No, there is inadequate attention paid to dose-response relationships, for both human and animal data. This is a major deficiency. For human studies, the results of any effects by duration or frequency of use, or other semi-quantitative measures are sometimes shown in the tables, but are not described or discussed in the text. In addition, I suspect that where the tables do not show effects by duration or frequency, this information may have been available in some of the studies (I'm thinking in particular of the Agricultural Health Study, where that type of information is available). If this is the case, then any such results should be added to the tables. Some studies also conducted tests of trend of incidence across these semi-quantitative exposure categories, and these results are also important in gleaning or refuting an effect.

The situation is similar in the animal studies. I assume that dose-response trends were evaluated in some of the studies; these results should be shown, where provided. Dose-response trends are readily calculable, and such results were presented in the IARC monograph. Even if dose-response trends were not tested, it is informative to know the incidence (as %s) at each dose level. This can contribute to inference about effects and whether they are causal."

RESPONSE: *ATSDR strives to make Toxicological Profiles both concise and informative. In an effort to reduce text, dose responses for both human studies and animal studies are reported in table format to allow the reader to access the data in a visual format and synthesized in the text. Animal dose response data can be found in tables located in Section 2.1. For example, a positive dose response for lower body weight was observed in male mice exposed to technical glyphosate after 13-week oral exposure with a NOAEL at 2,273 mg/kg/day and LOAEL at 4,776 mg/kg/day. Similarly, tables in Section 2.19 present dose-response findings for epidemiological studies. For instance, the relative risk for the highest quartile was reported as well as a p-trend for the outcomes in the Andreotti et al. (2018) study. All information for categorizing glyphosate exposure presented by authors of epidemiological studies were included in tables under the "Exposure" category. In incidences where multiple outcomes and categories of exposure were presented, ATSDR elected to report the estimates for the most descriptive and highest exposure category for each outcome to maintain a manageable table length.*

Question: Has the animal data been used to draw support for any known human effects? If so, critique the validity of the support.

The Reviewer stated "The results from the human and animal studies are described within the same sections, for each endpoint. I find reading the results together to be helpful in gleaning an overall effect. However, the text is not very rich in drawing connections or support between the animal and human data. This may be because the conclusion of this review is that there are no known health effects."

RESPONSE**:** *Animal studies typically employed exposure levels many times greater than those likely to be experienced by glyphosate-exposed humans. Available data for the general population provide insufficient evidence of adverse noncancer effects, thus precluding making connections between humans and animals regarding noncancer effects. With respect to cancer, ATSDR does not draw conclusions, but rather relies on well-established national and international sources. ATSDR has included summary information for publicly available human and animal carcinogenicity data.*

<u>Mechanisms of Action</u>

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

The Reviewer stated "No. In most of the health effect sections, possible mechanisms of action are not discussed at all. For example, I see no discussion of mechanisms for body weight effects."

RESPONSE**:** *A Mechanisms of Action Section (Section 2.21) was added to the profile.*

<u>Hazard Identification/Systematic Review Information</u>

Question: Are the hazard identifications clear and justifiable based on ATSDR's SR process? (In other words, if you follow ATSDR's SR protocol from start to finish, would you come to the same hazard identification conclusions?) If not, discuss where in the process there was a deviation from the protocol.

The Reviewer stated "It is not completely clear what is meant by the terminology of 'the hazard identifications', but I assume this refers to the health effects that were identified from the literature review that are listed in bullets at the start of Chapter 2. I believe that if I followed ATSDR's SR search protocol, I would come up with essentially the same list of studies on health effects of glyphosate (with 1

or 2 exceptions). I cannot comment on whether I would come to the same hazard identification conclusions without having reviewed all the literature myself. Nevertheless, the hazards identified appear clear and justifiable based on ATSDR's review. The ATSDR SR process is not fully described in the document or in the appendices, so I cannot comment on whether there was a deviation from the protocol."

***RESPONSE*:** *To increase transparency, ATSDR has recently initiated systematic review methodology into toxicological profile development. In some cases, only a limited systematic review may be feasible or necessary. When ATSDR began developing the Toxicological Profile for Glyphosate, systematic review had not been incorporated into the guidance. Thus, development followed our standard guidance, with the exception of the literature search framework which is presented in Appendix B.*

Question: Do you agree with the selection of endpoints that was carried forward through the SR process? If not, please indicate which endpoints you think should or should not have been included and why."

The Reviewer stated "The list of endpoints included in the search appears adequate."

***RESPONSE*:** *No response is necessary.*

Question: Do you agree with the SR framework as presented in Appendix B? Are there any steps that need to be revised? Please offer any suggestions to improve the utility, effectiveness, or clarity of the SR Framework.

The Reviewer stated "The SR framework is described as an eight-step process; however, these 8 steps are not shown in Appendix B. Appendix B shows the framework for the literature search and selection; it does not contain any information/framework about the methodology for the systematic literature review, per se. The entire SR framework should be outlined here, so the reader can understand the basic approach for hazard identification conclusions."

RESPONSE: *The Toxicological Profile for Glyphosate did not incorporate all eight steps of systematic review because the agency was in the process of implementation when the profile was initiated and had not yet incorporated all aspects into the guidance. The profile did include the first steps of problem formulation and literature strategy, which is presented in Appendix B.*

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

Section 3.1 TOXICOKINETICS

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

The Reviewer stated "Yes."

***RESPONSE*:** *No response is necessary.*

Question: Have the major organs, tissues, etc. in which the substance is stored been identified? If not, suggest ways to improve the text.

The Reviewer stated “Yes”.

RESPONSE**:** *No response is necessary.*

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

The Reviewer stated “Yes.”

RESPONSE**:** *No response is necessary.*

Question: Is there adequate discussion of the differences in toxicokinetics between humans and animals? What other observations should be made?

The Reviewer stated “Yes.”

RESPONSE**:** *No response is necessary.*

Question: Is there an adequate discussion of the relevance of animal toxicokinetic information for humans? If not, please explain.

The Reviewer stated “Yes.”

RESPONSE**:** *No response is necessary.*

Question: If applicable, is there a discussion of the toxicokinetics of different forms of the substance (e.g., inorganic vs. organic mercury)?

The Reviewer stated “Yes.”

RESPONSE**:** *No response is necessary.*

Section 3.2 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?

The Reviewer stated “I am not aware of any other data relevant to child health and developmental effects that have not been discussed in the profile and should be; however, I cannot answer this question with certainty without conducting a literature review myself.”

RESPONSE**:** *No response is necessary.*

Question: Are there any general issues relevant to child health that have not been discussed in the profile and should be?

The Reviewer stated "One aspect that is especially relevant to child health with regards to glyphosate is that children working in agricultural settings are likely to have high-end exposures, such as children of migrant farmworkers or children residing on a farm. The potential implications of these exposure issues are not discussed."

RESPONSE: *A statement in Section 5.7 was revised to read "Farm workers, farming families, and people of all ages living and or working in agricultural sectors will incur higher exposure to glyphosate, as agriculture is the largest industry for herbicide use." Animal studies have not provided convincing evidence for increased susceptibility of children to glyphosate toxicity. Limited data do not suggest that glyphosate would accumulate in breast milk. Health effects that have been demonstrated in animals occurred at doses many times greater than exposure levels expected among the general population. It appears sufficient at this time to simply state that families living on or near farms on which glyphosate is applied will incur higher levels of exposure to glyphosate.*

Question: If you answer yes to either of the above questions, please provide any relevant references.

The Reviewer stated "Not applicable."

RESPONSE: *No response is necessary.*

Question: Is there a discussion of populations at higher risk because of biological differences that make them more susceptible? Do you agree with the choices of populations? Why or why not? Are you aware of additional studies in this area?

The Reviewer stated "No such higher-risk populations were identified."

RESPONSE: *No response is necessary.*

Section 3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Question: Are the biomarkers of exposure specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?

The Reviewer stated "There is a biomarker of effect specifically for glyphosate, as well as a biomarker for the glyphosate metabolite, AMPA."

RESPONSE: *Detection of glyphosate or AMPA in blood or urine may be considered a biomarker of exposure to glyphosate, not a biomarker of effect. However, glyphosate undergoes so little metabolism in the body that detecting AMPA is unlikely.*

Question: Are there valid tests to measure the biomarker of exposure? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.

The Reviewer stated "Yes, there are valid tests to measure the biomarker, and this is consistent throughout the text.

RESPONSE: *No response is necessary.*

Section 3.4 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? If not, please clarify and add additional references.

The Reviewer stated "A possible interaction between glyphosate and surfactants such as POEA was identified. However, there is inadequate discussion of the interactive effects in the text. The same 1-3 studies are cited throughout (although only Adam et al. 1997 is listed here), with little explanation. A thoughtful summary of the evidence for this interaction is warranted (in addition to the results of the individual studies that were already described). Also, more information or discussion would be beneficial here regarding any known effects of POEA or mechanistic information about why synergism may occur."

RESPONSE: *No data were located to suggest a synergistic effect with substances in glyphosate formulations. Available data have only demonstrated that surfactants in glyphosate formulations are toxic in the presence or absence of glyphosate.*

Question: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? If not, please clarify and provide any appropriate references.

The Reviewer stated "No, the mechanism of the interaction was not discussed. I do not know of any appropriate references, offhand."

RESPONSE: *No data were located to suggest a synergistic effect with substances in glyphosate formulations. Available data have only demonstrated that surfactants in glyphosate formulations are toxic in the presence or absence of glyphosate.*

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

Question: Are you aware of any information or values that are wrong or missing in the chemical and physical properties tables? Please provide appropriate references for your additions or changes.

The Reviewer stated "No."

RESPONSE: *No response is necessary.*

Question: Is information provided on the various forms of the substance? If not, please explain.

The Reviewer stated "Yes, information is provided on both glyphosate and glyphosate isopropylamine salt."

RESPONSE: *No response is necessary.*

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

Section 5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Question: Are you aware of any information that is wrong or missing? If so, please provide copies of the references and indicate where (in the text) the references should be included.

The Reviewer stated "No."

RESPONSE: *No response is necessary.*

Sections 5.3-5.7

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.

The Reviewer stated "Yes, the text has appropriately traced the substance from its point of release until it reaches the receptor population. The occurrence of glyphosate at NPL sites is not known to be relevant at this time. No, I do not know of any other relevant information."

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.

The Reviewer stated "Yes. No I do not know of any other relevant information."

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.

The Reviewer stated "Yes. The information on page 118 and in Table 5-6 should be further explained. The study setting and conditions for the sampling conducted are not clear. For example, it would be relevant if these samples were taken from an agricultural region. It would also be very informative to know the number of samples collected in each instance, in order to understand the potential variability. Some of the units are not clear on page 118.

A table with the levels of glyphosate residue measured in different foods would be very informative (similar to the tables presented for the other media), particularly since there are a lot of different food types and it would be helpful to compare results by food type across different databases.

No I do not know specifically of any other relevant information."

RESPONSE: *Units in Section 5.5 were reviewed and necessary corrections were made. The available source for data in Table 5-6 did not include information regarding numbers of samples and specific locations of sampling. The statement in Section 5.5.4 regarding glyphosate concentrations in a variety of foods was revised to state "Glyphosate concentrations found in edible food treated with formulations of the glyphosate herbicide, Roundup, ranged from undetectable, ≤0.05 mg/kg, in several foods like bananas and selected meats to 3.7 mg/kg in a variety of grains and grain-based products (FAO 2005; FAO and WHO 2016)."*

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?

The Reviewer stated "Yes, the text describes 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. It would be informative to add information on detection of glyphosate and/or AMPA in urine from general population samples (as described for farming populations). No I do not know specifically of any other relevant information."

RESPONSE: *No information was located regarding measured levels of glyphosate and/or AMPA in urine samples from the general population.*

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 6.1 INFORMATION ON HEALTH EFFECTS

Question: Do you know of other studies that may fill a data gap? If so, please provide the reference.

The Reviewer stated "No."

RESPONSE: *No response is necessary.*

Section 6.2 IDENTIFICATION OF DATA NEEDS

Question: Are the data needs presented in a neutral, non-judgmental fashion? Please note where the text shows bias.

The Reviewer stated "I disagree with the blanket statement that epidemiological studies are "of limited usefulness for human health risk assessment." (line 31) These studies are extremely useful for hazard identification, which is essentially the goal of this document. Furthermore, I disagree that epidemiology studies should be interpreted cautiously given lack of monitoring data to quantify exposure; quantitative exposure measures can be constructed without using monitoring data (line 18, pg 136). Also, the call for a need for mode of action seems out-of-place in the Epidemiology section."

RESPONSE**:** *The sentence "They are of limited usefulness for human health risk assessment" was deleted.*

Question: Do you agree with the identified data needs? If not, please explain your response and support your conclusions with appropriate references.

The Reviewer stated "I agree with the need for human and animal studies with airborne (inhalation) exposures. Also, I would suggest to call for human studies for oral exposure, and not solely rely on the animal studies of oral exposure. Results in animals may differ from results in humans, and the oral pathway is likely to be the most relevant exposure route for the general population (through diet and water).

In addition, the information on 'non-persistence' of glyphosate seems questionable, given detections in many surface and groundwaters sampled. Data/testing on persistence in the environment should be conducted."

RESPONSE**:** *The following statements were added to the data needs section: "Humans should continue to be monitored for possible associations between glyphosate intake from food sources and adverse health outcomes" and "Additional studies should be designed to further assess potential for glyphosate to persist in foods, water, and soil."*

Question: Does the text indicate whether any information on the data need(s) exist(s)?

The Reviewer stated "No."

RESPONSE: *No response is necessary.*

Question: Does the text adequately justify why further development of the data need(s) would be desirable; or, conversely, justify the "inappropriateness" of developing the data need(s) at present? If not, how can this justification be improved.

The Reviewer stated "Yes, this is adequately justified."

RESPONSE: *No response is necessary.*

CHAPTER 7. REGULATIONS AND GUIDELINES

Question: Are you aware of other regulations or guidelines that may be appropriate for the table? If so, please provide a copy of the reference.

The Reviewer stated "No."

RESPONSE: *No response is necessary.*

CHAPTER 8. REFERENCES

Question: Are there additional references that provide new data or are there better studies than those already in the text? If so, please provide a copy of each additional reference.

The Reviewer stated "I mentioned a few other studies that provide new data or additional data (under Chapter 2). These studies are unlikely to change the conclusions of this review."

RESPONSE: *ATSDR has requested the mentioned studies and has performed update searching through September 2017 to identify and include recent data. All relevant data were included in subsequent drafts of the toxicological profile for glyphosate.*

Reviewer #3 peer-reviewed the following 3 unpublished sources for information in the Toxicological Profile for Glyphosate and provided comments on each source:

Agrisolutions. 2010. 62% Glyphosate IPA. Manufacturing concentrate. Submitted to the U.S. Environmental Protection Agency under FIFRA. https://www3.epa.gov/pesticides/chem_search/ppls/001381-00245-20101027.pdf. April 18, 2017. [Unpublished study to be peer reviewed]

The Reviewer stated "This document (Agricolutions 2010) is not a 'study'; rather, it is the EPA notice of registration for 62% glyphosate IPA, from 2010. Therefore, there is no design, and no methodology, reporting, or conclusions."

RESPONSE: *No response is necessary.*

Alferness PL. 1994. Volume 2. Touchdown: Determination of glyphosate and aminomethylphosphonic acid in corn grain, corn forage, and corn fodder by gas chromatography and mass-selective detection. Submitted under FIFRA to the U.S. Environmental Protection Agency. RR 92-042B. https://archive.epa.gov/pesticides/methods/rammethods/web/pdf/1994_055m.pdf. April 10, 2017. [Unpublished study to be peer reviewed]

The Reviewer stated "This document details a method for analysis of glyphosate and AMPA residues in corn commodities; however, it appears that only measurement of residues at 0.05 and 0.50 ppm are validated. The document contains detailed methodology of the equipment and procedures required, as well as an example of data from measurement in corn grain, corn forage, and corn fodder. I do not have the expertise to critique the design or methodology of this assay. Nor do I have different conclusions from the author."

RESPONSE: *No response is necessary.*

Pioneer. 2006. Early food safety evaluation for a glyphosate n-acetytransferase protein: GAT4601. Pioneer. A DuPont Company. Submitted to FDA under FDA's guidance for industry: Recommendations for the early food safety evaluation of new non-pesticidal proteins produced by new plant varieties intended for food use. https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=npc. April 10, 2017.

The Reviewer stated "This is a study of the allergenicity of synthetic glyphosate acetyltransferase (GAT) proteins in glyphosate-ready crops. This study seems inapplicable to the review, as it is not a study about glyphosate, but rather, about a synthetic protein. The authors conclude that "we have determined that the

GAT4601 protein is unlikely to cause an allergic reaction in humans of be a toxin in humans or animals." I disagree with such a broad conclusion based on the research they conducted. For example, they screened the bioinformatic databases for information on acute toxicity, therefore, it's a stretch to say more broadly that the protein is 'unlikely to be a toxin'. While the use of the bioinformatics tools for screening similarity to allergens and toxins appears appropriate, there is really no substitute for testing in human subjects to understand the reactions to a new protein."

RESPONSE: *No response is necessary.*

Reviewer #3 Specific Comments on Annotated Pages of the Toxicological Profile for Glyphosate

COMMENT: P12, L22: The Reviewer stated "Does this reference actually show data indicating lack of environmental persistence? Because none of the information provided in this report actually cites data showing lack of persistence."

RESPONSE: *The word "persistence" was replaced with "bioavailability."*

COMMENT: P12, L32: The Reviewer stated "Provide some indication of the widespread detection of glyphosate residues in many food products."

RESPONSE: *The following was added: "As a result of its widespread usage, glyphosate is present at low levels in a wide range of foods (FAO and WHO 2016)."*

COMMENT: P13, L28-29: The Reviewer suggested adding the following: "In addition, human (epidemiology) studies have reported on the association between glyphosate herbicide use and various health outcomes."

RESPONSE: *The following was added to the text that deals with human exposure: "Human studies have reported on possible associations between glyphosate herbicide use and various health outcomes."*

COMMENT: P13, L30-31: The Reviewer stated "It is a serious omission not to include the findings for glyphosate formulations. If not relevant or informative, then why were these studies reviewed at all?"

RESPONSE: *The following statement was added: "Furthermore, glyphosate formulations vary in specific components and their relative proportions, thus precluding meaningful comparisons of toxic effect levels." A thermometer graph of effect levels for glyphosate formulations is considered meaningless for the intended purpose of such graphs.*

COMMENT: P17, L1: The Reviewer stated "Edit the grammar."

RESPONSE: *The grammar was fixed.*

COMMENT: P17, L2: The Reviewer stated "Add the study of renal tubule dilation in offspring of dosed mothers. (the one that the EPA RfD is based on)."

RESPONSE: *The suggested addition was not made because, as noted in Chapter 2, EPA considered the result to be spurious because it was not observed in a 2-generation study that employed a 10-fold higher dose level.*

COMMENT: P17, L7-9: The Reviewer suggested adding references to the statements regarding associations between exposure to glyphosate and risk of non-Hodgkin's lymphoma.

RESPONSE: *Addition of a string of references would detract from the intent of this section. The reader can find detailed information in Chapter 2.*

COMMENT: P17, L29-32: The Reviewer suggested adding the following text to discussion of conclusions of the various agencies and organizations regarding glyphosate carcinogenicity: "These various evaluations provide different types of determinations – some focused on hazard identification, or whether there is evidence that an agent (chemical) can cause an effect, and others focused on carcinogenic risk, or the likelihood of a cancer effect at levels of exposure typically experienced by humans."

RESPONSE: *This section of the toxicological profile is intended to present a brief summary of conclusions. More detailed discussion of the human data is reserved for Chapter 2. The suggested addition was not made.*

COMMENT: P20, L14: Regarding the boilerplate statement that information is organized by health effect to help public health professionals and others address the needs of persons living or working near hazardous waste sites, the Reviewer stated "This may be a goal of this chapter, but the utility of organization by health effect for this purpose is not obvious. Organization by health effect is useful for many other reasons/uses."

RESPONSE: *Organization by health effect should be useful for any purpose.*

COMMENT: P20, L16: Regarding the description of exposure duration in units of "days", the Reviewer stated "Human days? Or same classification if in animal studies?"

RESPONSE: *The durations are species independent.*

COMMENT: P22, 4-6: Regarding the statement that surfactants in glyphosate formulations are at least partly responsible for the toxic effects from exposure to glyphosate formulations, the Reviewer indicated that ATSDR considers this to be the case and suggested revising the statement to note this.

RESPONSE: *The suggested addition was not made. Results from one study clearly demonstrate a toxic effect of the surfactant in a particular glyphosate formulation and provide indication that the effect of the surfactant was greater than that of glyphosate alone or in the formulation.*

COMMENT: P22, L17-19: Regarding the statement "Most reliable health effects data…", the Reviewer stated ""reliable" here is vague. Does it mean repeatable? Because that does not seem to be the case from the data. These studies certainly do have the most reliable dosing."

RESPONSE: *The statement was revised to read "Most reliable dose-response health effects data come from oral studies of animals administered glyphosate technical…"*

COMMENT: P22, 19-21: The Reviewer stated "Does this sentence belong here? The paragraph introduces animal studies of glyphosate technical, but this sentence about inhalation seems to refer to both gly technical and formulations."

RESPONSE: *The statement was intended to include both.*

COMMENT: P23, L10: Regarding the statement "Glyphosate is presently being re-evaluated for potential to cause cancer", the Reviewer stated "Re-evaluated by whom? But what do the available oral animal studies show? I'm sure some of these other endpoints are also being re-evaluated, but I thought this section was supposed to give an overall perspective on health effects (even uncertain effects)."

RESPONSE: *The statement was revised to state "Upon evaluation of available carcinogenicity studies in laboratory rodents, most agencies or organizations have concluded that glyphosate technical does not appear to be an animal carcinogen. In contrast, the International Agency for Research on Cancer considered the animal data to provide "sufficient evidence" of glyphosate carcinogenicity."*

COMMENT: P23, L13-14: Regarding the statement "Results from available animal studies identify the following targets of toxicity", the Reviewer stated "What about studies of cancer endpoint for glyphosate-based formulations? George et al. 2010; Seralini et al. 2014."

RESPONSE: *The study of Seralini et al. (2014) was retracted. The study of George et al. (2010) has been requested and will be evaluated for possible inclusion in future drafts of the toxicological profile for glyphosate.*

COMMENT: P25, Figure 2-2: The Reviewer stated "These text colors aren't very distinguishable. In the figure, the contrast is fine."

RESPONSE: *The depiction of humans versus animals has been revised to more clearly provide distinction between the two.*

COMMENT: P25, Figure 2-2, footnote: Regarding the statement "Exposure route and duration information was not available for humans", the Reviewer stated "This is not actually true; a few of the human studies evaluated risk by duration of use."

RESPONSE: *The statement was revised to read "Reliable exposure route and duration information was not typically available for humans."*

COMMENT: P26, Table 2-1, Figure key 3: Regarding reference to 28.5% depressed mean body weight, the Reviewer stated "Is this maternal body weight gain? I don't see how this differs from fetal body weight, below."

RESPONSE: *The statement was revised to read "28.5% depressed mean maternal body weight."*

COMMENT: P26, Table 2-1, Figure key 3: Regarding the classification of diarrhea as a serious effect, the Reviewer stated "Should this be 'Less Serious'?"

RESPONSE: *No, because it occurred at a maternally-lethal dose.*

COMMENT: P26, Table 2-1, Figure key 3: Regarding the classification of 9% depressed mean fetal body weight as a "less serious" effect, the Reviewer stated "This fetal body weight depression should be "Serious" (as is the maternal body weight depression, above. It seems that any fetal weight depression is serious."

RESPONSE: *The effect was not of sufficient magnitude to be considered a "serious" effect.*

COMMENT: P27, Table 2-1, Figure key 5: Regarding the classification of up to 14-20% depressed mean pup body weight or body weight gain during lactation at maternally-toxic dose level, the Reviewer stated "It is not clear why weight loss/lack of weight gain is sometimes classified as less serious, otherwise as serious. Is it based on the % of animals experiencing the effect?"

RESPONSE: *The effect was changed to "serious."*

COMMENT: P27, Table 2-1, Figure key 7: The Reviewer stated that it was not accurate to identify a NOAEL of 30 mg/kg/day for developmental effects because the study reported renal tubule dilation in offspring.

RESPONSE: *The endpoint was deleted because although the finding of renal tubule dilation in the F3b male offspring was likely a spurious result, there is some degree of uncertainty. Therefore, ATSDR has elected not to identify a NOAEL or LOAEL for developmental effects.*

COMMENT: P30, Table 2-1, Figure key 13: Regarding the effect of centrilobular hepatocellular necrosis being listed as a "less serious" effect, the Reviewer stated "Should this be listed as 'serious'?"

RESPONSE: *The effect was changed to "serious."*

COMMENT: P30, Table 2-1, Figure key 15: Regarding the statement of 13% lower mean body weight at treatment week 81, the Reviewer stated "The length of followup at which body weight was decreased is not noted for all studies in this table."

RESPONSE: *This is because magnitude of depressed body weight in this study exceeded 10% only at week 81.*

COMMENT: P33 and 35, Figure 2-3: The Reviewer questioned why MRLs were plotted.

RESPONSE: *The MRL plots are in error and were deleted.*

COMMENT: P36, Table 2-2, Figure key 1: The Reviewer questioned why diarrhea was listed as a "serious" effect.

RESPONSE: *Because it increased in severity with time and the dose level was also lethal to some rats.*

COMMENT: P37, Table 2-2, Figure key 9: The Reviewer agreed with the 60-66% depressed mean body weight gain designation of "serious", but asked why.

RESPONSE: *Because of the magnitude of the effect (60–66% depression).*

COMMENT: P44, Table 2-4: The Reviewer stated "Where not shown, do the studies show effects by duration or frequency of use, cumulative use, or other semi-quantitative measures? I'm thinking in particular of the Agricultural Health Study, where they have that type of information available."

RESPONSE: *Most studies summarized in Table 2-4 reported exposure in terms of ever exposed during a lifetime. Where additional exposure period and/or frequency data were available, such information was added to the table.*

COMMENT: P44, Table 2-4, Hoppin et al. 2002 entry: The Reviewer stated "Be more specific about the exposure metric used in each study. Essentially everyone is exposed to glyphosate (i.e. from trace amounts in the diet and drinking water) so "any glyphosate exposure" is meaningless. I believe for most of these studies, the variable is 'ever used glyphosate'."

RESPONSE: *Each study was reviewed and more explicit exposure metric information was added to Table 2-4*

COMMENT: P44, Table 2-4, Hoppin et al. 2002 entry: Regarding the statement in the "Outcome" column, the Reviewer stated "The study says in the text 'When chemicals commonly applied together and crop and animal-related exposures were included in the same model, the results were essentially the same as those reported in Tables 2 and 3'. So, with adjustment for other pesticides, I assume the trend was significant, similar to that shown here."

RESPONSE: *It seems like a logical assumption, although quantitative data to support the assumption were not included in the study report.*

COMMENT: P49, Table 2-4, Sathyanarayana et al. 2010 entry: Regarding the data in the "Outcome" column, the Reviewer stated "Is the upper CL at +48g? Use of a dash makes it confusing. I'd suggest a comma."

RESPONSE: *The range was changed to read "-40 to +48 g."*

COMMENT: P50, L2: The Reviewer asked whether the glyphosate was glyphosate technical.

RESPONSE: *The word "technical" was added.*

COMMENT: P50, L1-10: The Reviewer stated that the effects in the study of Adam et al. (1997) are definitely serious effects which are not in results summarized in tables or figures.

RESPONSE: *Intratracheal instillation is not a natural exposure route. Therefore, the result is not listed in LSE tables or figures for inhalation, oral, or dermal exposure.*

COMMENT: P51, L27: The Reviewer asked whether the gastrointestinal effects in the gavage study of Adam et al. (1997) were included in the LSE table.

RESPONSE: *Yes; however, the dose of 3,000 mg/kg was in error and was corrected to 2,000 mg/kg.*

COMMENT: P53, L19: The Reviewer stated "This section on renal effects does not include the Monsanto 1981 study that saw renal tubule dilation in male offspring of mice dose with 30 mg/kg/day; this is the study on which the EPA oral RfD is based. Why is this study not included here? I see the study is listed below under 'Developmental Effects', but would it not be more appropriate here?"

RESPONSE: *No, the effect would be developmental since the mice were exposed via their mothers.*

COMMENT: P53, L30-31: The Reviewer stated "The kidney weight change may be a treatment-related effect (no evidence that it's not), but I believe the point here is that ATSDR doesn't consider it to be an 'adverse' effect, since there was no evidence of histopathologic kidney lesions."

RESPONSE: *The phrase "treatment-related" was deleted.*

COMMENT: P54, L11-13: The Reviewer suggested that a statement be added indicating that the result of Tizhe et al. (2014) is not included in the LSE table.

RESPONSE: *The following statement was added: "Therefore, the study is not summarized in the oral LSE table or figure."*

COMMENT: P55, L22-23: Regarding the lack of evidence for endocrine effects in animal studies, the Reviewer stated "This endpoint doesn't show up in the table. It is not even shown as one of the measured endpoints or parameters monitored in the study."

RESPONSE: *The statement regarding the lack of evidence for endocrine effects was revised to state "Available animal studies do not include adequate assessment of glyphosate technical treatment-related effects on the endocrine system.*

COMMENT: P57, L18-20: Regarding the statement See Section 2.17 for information regarding treatment-related effects on the reproductive system of male rats exposed to glyphosate formulations during in utero and/or postnatal development", the Reviewer stated Result in Cassault-Meyer 2014 is listed as reproductive but is not listed here (saw abnormal sperm morphology at 640 mg/kg/day). Dallegrave

2007 saw decreased sperm production at 50 mg/kg/day, which seems appropriate to list as 'reproductive', although this result is categorized as 'developmental'."

RESPONSE: *The findings of Cassault-Meyer et al. (2014) were added to the reproductive toxicity section of the text. The results of Dallegrave et al. (2007) are listed under developmental effects because exposure occurred via their mothers during gestation and lactation.*

COMMENT: P57, 31-32: The Reviewer stated "Isn't miscarriage the same outcome as spontaneous abortion?"

RESPONSE: *The term "spontaneous abortion" was parenthetically added to the first instance of the term "miscarriage."*

COMMENT: P57, L33-35: The Reviewer asked whether "deficits" should be "defects."

RESPONSE: *Yes, the correction was made.*

COMMENT: P58, L2-4: The Reviewer asked for explanation as to why the animal data are not sufficient to draw conclusions regarding glyphosate-induced developmental effects.

RESPONSE: *The statement in question was deleted.*

COMMENT: P58, L8-11: The Reviewer stated "Other studies, when conducted separately, are treated as independent results in this ATSDR Tox Profile. Why is the 2nd of these 2 studies used to interpret the first?"

RESPONSE: *Because the second study was of similar design to the first study, but included a dose group 10-fold higher than the high dose of the first study and did not observe effects on the kidney. Furthermore, the 3-generation study reported increased incidence of kidney tubular dilation only in male weanlings and only one generation (F3b) of 6 total generations of pups evaluated (F1a, F1b, F2a, F2b, F3a, F3b).*

COMMENT: P59, L8-9: Regarding the statement: "The results of these studies should be interpreted cautiously given the lack of monitoring data to quantify glyphosate exposure and the likely exposure to other pesticides.", the Reviewer stated "This is not a reason to interpret the data cautiously. Adequate semi-quantitative exposure metrics can be constructed in epidemiologic studies, even without monitoring data."

RESPONSE: *This section was extensively revised and no longer includes the statement in question.*

COMMENT: P59, L21-26: The Reviewer stated "Explain that the designation of 'no association' is based on statistical significance, defined with a p- value cutoff of <0.05."

RESPONSE: *This section was extensively revised and includes the risk values with 95% confidence intervals from each study summarized in this section.*

COMMENT: P59, L27-29: The Reviewer stated "There was a positive association in McDuffie with >2 days use per year. Why does this section only report on results of ever/never, when a few studies looked at duration or frequency? (De Roos 2005, McDuffie, Eriksson)"

RESPONSE: *This section was extensively revised and the positive association in the McDuffie et al. (2001) study was added.*

COMMENT: P59, L29-32: Regarding the statement that indicated associations between glyphosate and non-Hodgkin's lymphoma risk were no longer found after adjustment for exposure to other pesticides; the Reviewer stated "This is not true. De Roos et al. 2003 saw an association with adjustment for multiple other pesticides."

RESPONSE: *This section was extensively revised. The summary of results from De Roos et al. (2003) was included to note a significant association using logistic regression and the lack of a significant association using hierarchical regression.*

COMMENT: P60, Table 2-5 Solid tumor summary entry for De Roos et al. (2005a): The Reviewer questioned: "Why are certain cancer results shown, but not others?"

RESPONSE: *All solid tumor types were included in the summary and are present in the revised section. Lymphohematopoietic tumor results are found in a separate table section.*

COMMENT: P69, Table 2-6, non-Hodgkin's lymphoma entry for IARC (2016). Regarding the RR and 95% CI, the Reviewer stated: "Why does this differ from Schinasi and Leon 2014 if it includes the same studies? Explain briefly in text."

***RESPONSE*:** In the extensively revised text, the following statement was made: "The IARC Working Group conducted a meta-analysis for NHL using the same six studies as Schinasi and Leon (2014) and Chang and Delzell (2016). The Working Group reanalyzed the data but used the most fully adjusted risk estimates for the studies by Hardell et al. (2002) and Eriksson et al. (2008)."

COMMENT: P69, Table 2-6, non-Hodgkin's lymphoma entry for Chang and Delzell (2016). The Reviewer stated: "Does this paper simply reference the IARC 2016 meta-analysis?"

RESPONSE: *No, this was a separate evaluation.*

COMMENT: P70, L13-15: The Reviewer asked why the range of 3.4-6.7% is different from the range of 0-12% in the earlier portion of the sentence.

RESPONSE: *Because the former range (0–12%) is for historical controls and the other range (3.4–6.7% is for controls from those 26-month studies performed concurrently with the study summarized by EPA (1992d).*

COMMENT: P70, L16-18: The Reviewer stated "Statements from this EPA 1992 document have been cited several times. Makes this seem like it's not an independent review." "Again, this is EPA's review of the study, not ATSDR's."

RESPONSE: *ATSDR can cite only publicly available studies. The original studies are proprietary studies and are therefore not citable. As noted in the introduction to Chapter 2, EPA produced Data Evaluation Records and other reviews of the animal carcinogenicity studies submitted to EPA in the product registration process. The EPA summaries cited in this toxicological profile are publicly available and are therefore cited.*

COMMENT: P70, L18 to P71, L1: The Reviewer stated "Some carcinogens do not cause preneoplastic or nonneoplastic lesions."

RESPONSE: *This section has been revised to state the following: "EPA (2015c) did not consider the increases of testicular interstitial cell tumors in the rats to be treatment-related based on the following weight-of-evidence considerations: (1) lack of dose-response; (2) absence of preneoplastic lesions; (3) incidences were within normal biological variation in the rat strain; (4) incidences in the concurrent controls (0%) was not representative of historical control incidences (range 3.4–6.7%); and (5) no interstitial cell tumors were seen in another study of the same rat strain at much higher dose levels (EPA 1991a, 1991b). The lack of preneoplastic lesions is only one of the considerations of EPA. The weight of evidence included all points listed above.*

COMMENT: P71, L1-2: The Reviewer is not interested in EPA's opinion on the testicular interstitial cell tumor incidences.

RESPONSE: *ATSDR does not disagree with EPA's conclusions. However, EPA had access to information that is not publicly available, thus precluding ATSDR's totally independent review.*

COMMENT: P71, Table 2-7: The Reviewer stated "I disagree with the use of historical control incidence here. Nevertheless, incidence in the high-dose group is almost double the high range of the historical control incidence, which seems like a convincing increase."

RESPONSE: *The incidence in the concurrent controls was 0%, which is much lower than incidences in the range of historical controls. The normal control incidence would have been in the range of 2/50 animals, in which case pairwise comparison between controls and high-dose groups would not have resulted in a statistically significant difference.*

COMMENT: P71, L7-8: Regarding the statement "Incidences of thyroid c-cell carcinomas in female rats were borderline significantly (p=0.055) increased at the highest dose (6/47 versus 1/47 for controls) (EPA 1992d). However, the incidence of combined c-cell carcinomas or adenomas was not significantly increased (9/47 high-dose females versus 6/47 controls).", the Reviewer stated "This convinces me more about the carcinogenicity, rather than detracting from the argument."

RESPONSE: *The statements were revised to note the facts without attempting to detract from the observed results.*

COMMENT: P72, L13-22: Regarding the EPA weight-of-evidence conclusions regarding the incidence of pancreatic islet cell tumor incidence, the Reviewer stated "Again, this explanation of EPA's opinions is not appropriate here, if this document is to stand as an ATSDR conducted review.

In addition, the EPA 2016a document appears to bring in multiple approaches to explain away any effect that was seen.

Adjustment for multiple comparisons is an artificial construct that is based on a subjective number of hypotheses being tested."

RESPONSE: *This section was revised to read "EPA (2015c) did not consider the pancreatic islet cell adenomas in the male rats to be treatment-related based on the following weight-of-evidence considerations: (1) although the incidences at the low and high dose levels exceeded the historical control range (1.8–8.5%), there was a lack of significant trend; (2) the tumor incidence in the concurrent control was at the low end of the historical control range; (3) lack of a dose-response characteristic; (4) no preneoplastic changes; (5) no progression from adenomas to carcinomas; and (6) the apparent statistical significance in pairwise comparisons between treated groups and concurrent controls may have been the result of low incidences in the control group. EPA (2015c) noted that subsequent rat studies did not find treatment-related effects on pancreatic islet cell tumors." The argument regarding multiple comparisons was removed. As stated previously, ATSDR does not disagree with EPA's conclusions. However, EPA had access to information that is not publicly available, thus precluding ATSDR's totally independent review.*

COMMENT: P75, L16-18: The Reviewer stated "My understanding is that IARC only reviews published, available studies as well, but their review included more studies."

RESPONSE: *The IARC assessment of glyphosate included summaries for a number of proprietary studies submitted by chemical companies to European agencies for the purpose of registering a product for use. These studies were not available to ATSDR. Some of these studies were made available to EPA. EPA produced "abbreviated Data Evaluation Records" for some of these studies. The publicly-available summaries of EPA have been added to the ATSDR toxicological profile for glyphosate in a separate table. The text was revised to note the addition.*

COMMENT: P76, L23-25: The Reviewer suggested changing the stated conclusion of FAO and WHO (2016) and noted that the risk may be there, but it's low based on dietary levels.

RESPONSE: *The statement was revised to read "The FAO/WHO Joint Meeting on Pesticide Residues concluded that glyphosate was unlikely to pose a carcinogenic risk to humans via exposure from the diet (FAO and WHO 2016)." The statement was taken verbatim from the document.*

COMMENT: P84, L15-19: The Reviewer asked for explanation of contradictory conclusions regarding the genotoxicity of glyphosate.

RESPONSE: *This section was revised to note the bottom-line conclusions of the various groups as to the genotoxicity of glyphosate and to refer the reader to the documents produced by these groups for detailed discussions.*

COMMENT: P92, L4-5: The Reviewer asked whether toxicity in the sentence "No information was located to suggest significant differences between animals and humans regarding glyphosate toxicity." Should be changed to toxicokinetics.

RESPONSE: *Yes, this change was made.*

COMMENT: P92, L23-24: Regarding the boilerplate statement "Populations at greater exposure risk to unusually high exposure levels to glyphosate…", The Reviewer stated "By definition they are at greater exposure risk…what this should refer to is health risks, correct?"

RESPONSE: *The statement was revised to read "Populations at risk of exposure to glyphosate at unusually high levels are discussed in Section 5.7, Populations with Potentially High Exposures."*

COMMENT: P92, L26-27: Regarding the statement "No information was located to indicate significant age- or gender-related differences in susceptibility to glyphosate toxicity.", the Reviewer stated "What about the fact that one of the lowest LOEALs is for male hormonal outcomes?"

RESPONSE: *The statement was revised to read "No information was located to indicate significant age- or gender-related differences in susceptibility to glyphosate technical toxicity. One study employed a glyphosate formulation as test substance and found decreased serum testosterone in young male rats gavaged at a dose as low as 5 mg/kg/day (Romano et al. 2010); however, the effect may have been caused, at least in part, by other ingredients in the glyphosate formulation."*

COMMENT: P94, L4-6: Regarding the statement "Surfactants such as POEA in glyphosate-containing products might enhance the toxicity of glyphosate; results from one study indicate that the surfactant may be more acutely toxic than glyphosate or the combination of glyphosate and POEA (Adam et al. 1997)", the Reviewer stated "Wasn't there >1 study indicating this interaction?"

RESPONSE: *The citation was revised to make clear it is an example.*

COMMENT: P98, L14-17: The Reviewer suggested adding "water" to the statement regarding coming into contact with crops or soils on which glyphosate-containing products have been applied.

RESPONSE: *The suggested addition was made.*

COMMENT: P102, L4: Regarding the statement "No information was found concerning U.S. imports and exports of glyphosate", the Reviewer stated "Based on what type of search? Are there vetted databases for this type of information? It seems it would be readily available if ATSDR routinely searches for this information for various chemicals for their Tox Profiles."

RESPONSE: *The following resources are listed in the ATSDR guidance for the import and export sections and were consulted for information on glyphosate:*

- *U.S. International Trade Commission (USITC),*
- *Stanford Research Institute, Incorporated (SRI) (Menlo Park, CA; Directory of Chemical Producers of the United States)*

- Chemical Marketing Reporter (CMR) (Schnell Publishing, New York, NY)
- Chemical and Engineering News (C&EN) (Facts and Figures for the Chemical Industry and Top 50 Chemical Products)
- U.S. Department of Interior, Bureau of Mines (Mineral Commodity Annual Summaries and Mineral Yearbooks)
- U.S. Department of Commerce (DOC) (U.S. general imports for consumption)
- Hazardous Substances Data Bank (HSDB)

COMMENT: P104, L3-15: Regarding the boilerplate text on TRI data, the Reviewer stated "This paragraph isn't relevant here since glyphosate isn't reportable to TRI."

RESPONSE: *It is true that there are no TRI data for glyphosate because facilities are not required to report releases of glyphosate. However, the boilerplate is common to all ATSDR toxicological profiles and subsequent text notes that facilities are not required to report releases to the environment.*

COMMENT: P116, Table 5-3: The Reviewer stated "I don't understand why the limit of detection differs for drinking water and surface water and groundwater. Should the limit of the detection be the same in water, whatever the source?"

RESPONSE: *Limits of detection vary according to sampling sources, sampling procedures, and analytical methods used.*

COMMENT: P116, Table 5-4: Regarding the statement "not detected" in drinking water, the Reviewer stated "Should this say 'not studied'? Otherwise, also include the reference or the Table number where the study(ies) are detailed."

RESPONSE: *Table 5-7 was added to point the reader to more information regarding levels measured in drinking water.*

COMMENT: P117, L1-3: Regarding the statement "A study by the USGS evaluated 3,732 environmental samples across 38 states from several studies examining glyphosate in the environment; the samples were collected between 2001 and 2010 from 1,341 different sites", the Reviewer stated "This is vague. Were they all water samples? Explain what the set of samples consisted of before launching into the paragraph. It would also be informative to know more about the sampling sites – mostly agricultural regions? Etc."

RESPONSE: *The statement was revised to note that sampling sites included groundwater; lakes, ponds, and wetlands; soil water; streams; large rivers; precipitation; ditches and drains; soil and sediment; and waste water treatment plant outfall.*

COMMENT: P117, L3-5: Regarding the statements "Glyphosate was detected in 39.4% of all the samples, with a median value of <0.02 µg/L and a maximum value of 476 µg/kg. Its degradation product, AMPA, was detected in 55% of all the samples, with a median value of 0.04 µg/L and a maximum value of 397 µg/kg", the Reviewer stated "This mixing of units is confusing. Either convert all values to one set of units, or speak about findings with different units in different sentences."

RESPONSE: *The units were corrected.*

COMMENT: P117, Table 5-5: The Reviewer suggested adding a column for the number of samples.

RESPONSE: *Table 5-5 was revised to more clearly present available data along with numbers of samples.*

COMMENT: P119, Table 5-6: The Reviewer suggested adding a column for the number of samples.

RESPONSE: *Table 5-6 was revised to more clearly present available data along with numbers of samples when available.*

COMMENT: P119, Table 5-6, first entry: The Reviewer stated that the geographic type identified as "finished water" should have been more descriptive. The Reviewer stated "Is this finished water from groundwater or surface water?"

RESPONSE: *The entry was deleted and the table title was revised to include only surface water monitoring data for glyphosate.*

COMMENT: P124, L8-12: Regarding presentation of concentrations of glyphosate in selected crops, the Reviewer stated "Are these the same samples measured at different times? Why do some of the levels increase?"

RESPONSE: *The various plant types were treated once with glyphosate and at each timepoint 4, 6, and 8 weeks posttreatment, one plant from each type was extracted and assessed for glyphosate residue. The up-and-down variation in levels over time is likely related to variability in bioavailability from the soil and root uptake.*

COMMENT: P126, L7: Regarding the statement "… this chemical has low leaching potential", the Reviewer stated "Don't follow - leaching from what?"

RESPONSE: *The text was revised to state "…this chemical has low leaching potential from soil to groundwater."*

COMMENT: P129, L1-2: The Reviewer stated "The attribution of health effects belongs in Chapter 2, not here."

RESPONSE: *The statement regarding medical outcomes was deleted. The study results were already reported in Chapter 2.*

COMMENT: P131, L31-32: Regarding the statement "They are of limited usefulness for human health risk assessment", the Reviewer stated "1) But this is not a full risk assessment; 2) human data can be very useful for hazard identification – the first step in a risk assessment. And as I understand it, this is a goal here."

RESPONSE: *The statement in question was deleted.*

COMMENT: P131, L32-33: Regarding the statement "Most reliable health effects data come from oral studies of animal examining potential body weight, gastrointestinal, hematological, hepatic, and developmental effects.", the Reviewer stated "'Reliable' in what way? If you mean 'repeatable' then this does not play out in the data." The Reviewer also stated "Why these outcomes? The other (mostly negative) effects from other outcomes were not considered reliable?"

RESPONSE: *The word "reliable" was deleted. The statement was revised to read "Most reliable health effects data come from animal studies that employed oral exposure and examined potential body weight, gastrointestinal, hematological, hepatic, and and/or developmental effects." The intent of this statement is to identify the most often evaluated endpoints (which are identified in Figure 6-1).*

COMMENT: P132, Figure 6-1 footnote: The Reviewer stated "Does it match the studies discussed in Chapter 2? I don't see why this needs to be presented again here unless it is different from Chapter 2; otherwise, explain explicitly what the difference is."

RESPONSE: *The study count information in Figure 6-2 is the same as that in Figure 2-2. Figure 6-2 would normally present human and animal counts by route of exposure. In the case of glyphosate, a specific exposure route is not available. For animal studies, data were available only for oral exposure. Otherwise, the presentation of data for Figure 6-2 would be different (count by would be by exposure route).*

COMMENT: P133, Figure 6-2: The Reviewer stated "Why are the human studies all categorized under 'inhalation', when it was previously stated that no information on route of exposure was available from the human studies. The route of exposure is likely dermal as well in studies of persons using/applying glyphosate."

RESPONSE: *The categorization of exposure route for the human studies was deleted.*

COMMENT: P134, L16: The Reviewer stated "Also seems relevant to call for human studies for oral exposure, and not solely rely on the animal studies of oral exposure. Results in animals may differ from results in humans."

RESPONSE: *The following statement was added to this section: "Humans should continue to be monitored for possible associations between glyphosate intake from food sources and adverse health outcomes."*

COMMENT: P135, L17-19: The Reviewer suggested using the phrase "quantitative or semi-quantitative glyphosate exposure information" rather than "monitoring data to quantify glyphosate exposure."

RESPONSE: *The suggested wording change and addition were made.*

COMMENT: P135, L22-25: The Reviewer suggested wording change and questioned the call for mode of action data in this section.

RESPONSE: *The entire statement from EPA (2016a) was deleted because the source is not citable, according to EPA.*

COMMENT: P136, L26-29: The Reviewer indicated that understanding of glyphosates behavior is not really the point in this sentence, but rather "The point is to understand better the total amount of bioavailable human exposure, so that the potential for health effects can be evaluated." The Reviewer suggested replacing "understanding of this chemical's behavior" with "potential for health effects."

RESPONSE: *The statement was revised to read "Investigative studies on the relative bioavailability of glyphosate in different environmental media, especially food for human consumption, would add considerable value to assessing potential for health effects."*

COMMENT: P137, L1: The Reviewer stated "I found the exposure data from waters, soils, and foods to be intriguing. Information on persistence of glyphosate in these media would be useful, particularly since glyphosate is often thought of as a 'non-persistent' pesticide."

RESPONSE: *The following statement was added to data needs for Environmental Fate: "Additional studies should be designed to further assess potential for glyphosate to persist in foods, water, and soil."*

COMMENT: P137, L2: The Reviewer stated "Were some of the exposure data (e.g., from USGS) from agricultural areas? If so, you could say there is a need for 'more data' here."

RESPONSE: *The statement already calls for monitoring data in environmental media surrounding areas where glyphosate products are applied. That naturally includes agricultural areas.*

COMMENT: P138, L8-10: Regarding the statement "No inhalation or oral MRLs were derived for glyphosate formulations due to variation in glyphosate content and surfactants used in various glyphosate formulations and the fact that surfactants contribute to the toxicity of glyphosate formulations.", the Reviewer stated "This is not a reason not to derive an MRL. From the animal studies, knowing the % glyphosate in the formulation, an MRL could be derived. It's true that surfactants may contribute to the toxicity of the glyphosate formulation, but the MRL is a MINIMUM risk level, not an exact risk level."

RESPONSE: *There are some data on GBFs, but not sufficient data to derive MRLs. The concentration of glyphosate in GBFs varies. GBFs also contain other additives (e.g., surfactants), and the data indicate that these additives may be more toxic than the active ingredient.*

COMMENT: P138, Table 7-1: The Reviewer asked for explanation of the difference between "not "evaluated" and "no data."

RESPONSE: *The terms are self-explanatory. It does not appear necessary to further describe them.*

COMMENT: P139, Table 7-1, footnote d: The footnote states "Group D not classifiable as to human carcinogenicity. Note: EPA's IRIS program has not planned to re-evaluate the potential carcinogenicity of glyphosate. EPA's Office of Pesticide Programs (EPA 2016a) re-evaluated available human and animal data regarding the potential carcinogenicity of glyphosate and concluded that the strongest support is for the descriptor "not likely to be carcinogenic to humans at doses relevant to human risk assessment." However, EPA has not completed its Registration Review for Glyphosate."

The Reviewer stated "The EPA OPP descriptor does not make sense according to their defined approach: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/evaluating-pesticides-carcinogenic-potential#terms

This states that a substance can be qualified as 'Not Likely to Be Carcinogenic' below a certain dose if a key event in tumor formation does not occur below that dose. However, in the case of glyphosate, there has been no discussion in this (ATSDR) document of the key events in tumor formulation.

Besides, what does 'at doses relevant to human risk assessment' mean? It was acknowledged that more data are needed on total human exposure (from all foods and water)."

RESPONSE: *The descriptor and text were taken from EPA (2015c) (EPA 2016a is not citable because it is not a final document). The descriptor was not changed.*

COMMENT: P139, Table 7-1, footnote d: Regarding the statement "However, EPA has not completed its Registration Review for Glyphosate", the Reviewer stated "It's really not appropriate to include this statement in a footnote, without discussion.

I also think it's not appropriate to include it at all, if EPA has not completed its review."

RESPONSE: *The statement in question was removed.*

COMMENT: A-1, L7: Regarding the boilerplate statement "MRLs are based on noncancer health effects only; cancer effects are not considered", the Reviewer stated "Because …. This implies no safe level for carcinogens (as is typical in risk assessment) and argues against the EPA 2016 re-registration conclusion of 'not likely to be carcinogenic' at certain dose levels."

RESPONSE: *The purpose of the statement is inform the reader that the MRLs only takes into consideration noncancer data. It does not make an implication of regarding whether there is a threshold for cancer. Hazard assessments evaluate the noncancer and cancer risks separately; thus, separate guideline values are typically derived for cancer and noncancer effects. ATSDR does not derive cancer guideline values.*

COMMENT: A-2, L17-22: Regarding the statements "The general population will not be exposed to glyphosate technical, but rather to glyphosate formulations registered for use. MRLs based on animal exposure to glyphosate technical would not adequately reflect human exposure to glyphosate formulations. Therefore, no MRLs were derived for glyphosate technical. No MRLs were derived for glyphosate formulations due to the wide variation in glyphosate content and surfactants used in various glyphosate formulations and the fact that surfactants contribute to the toxicity of glyphosate formulations", the Reviewer stated "This is a circular argument that circumvents the need for defining MRLs for either! Of course, exposures to glyphosate technical can be estimated from exposure to glyphosate formulations

based on %glyphosate and amount of exposure. This is certainly difficult to do in the human studies, but not in the animal studies."

RESPONSE: *Human exposure to GBFs via its use in weed control includes exposure to all substances in GBFs. No MRLs were derived for GBFs due to the wide variation in glyphosate content and surfactants used in various GBFs and the fact that surfactants can contribute to the toxicity of GBFs. However, the general population may also be exposed to glyphosate and/or its breakdown products by ingesting food or water in which glyphosate is detected. Therefore, health effects data from oral exposure to glyphosate technical are considered relevant to potential derivation of oral MRLs for glyphosate. ATSDR is considering whether to derive oral MRLs for glyphosate based on animal data for glyphosate technical; the results of this consideration will be applied to future drafts of the Toxicological Profile for Glyphosate.*

COMMENT: B-1 (title): The Reviewer stated "This appendix would more accurately be called 'Literature Search Framework…' rather than 'Literature Review…', since the methods/approaches for actually 'reviewing' the literature aren't outlined here."

RESPONSE: *The suggested change was made.*

COMMENT: B-1, Table B-1: Regarding the statement "parenteral (these studies will be considered supporting data", the Reviewer stated "Why supporting only?"

RESPONSE: *When parenteral injection studies provide strong support to a weak database of information from natural exposure routes, or when parenteral injection studies are the major source of information regarding potential mechanisms of action, such data would be considered for inclusion in toxicological profiles. When adequate data exist for natural routes of exposure, and results from parenteral exposure routes do not significantly impact conclusions, it may be considered unnecessary to include results from unnatural exposure routes.*

COMMENT: B-1, Table B-2 (Database search date): The Reviewer stated "Why was the search not updated to include papers published in the 2+ years since this initial search? Additional papers have been published – For example, Parks CG et al. Rheumatoid Arthritis in Agricultural Health Study Spouses: Associations with Pesticides and Other Farm Exposures."

RESPONSE: *Parks et all (2016) was added to the profile. An updated literature search was conducted for human cancer data and new literature was added to the profile. Another literature search will be conducted after the public comment period, before releasing the final document.*