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

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

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Comments Provided by Peer Reviewer #1

ATSDR Charge Questions and Responses

Glyphosate Technical MRLs

QUESTION: Do you agree that exposure to glyphosate technical is possible?

COMMENT: Yes. While most uses involve formulation products, human exposure in the diet and through water will be to glyphosate, either as the acid or anion. Similarly, exposure through the skin will often also be to glyphosate itself. As a result, I think it is appropriate to assess the toxicity of glyphosate technical.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree that ingredients and concentrations in glyphosate-based formulations differ too much to assess?

COMMENT: As indicated elsewhere (Henderson et al., 2010a), glyphosate is marketed in the United States and throughout the world in hundreds to thousands of products. It can be used as an acid or as various salts and in a range of formulation products containing various adjuvants and surfactants. Because of the wide diversity of products, it is not feasible to perform an assessment of the full range of glyphosate formulation products. Some products that were used in the past such as the trimesium salt form are no longer marketed. It is certainly less complicated to perform an assessment of glyphosate technical itself. I might note that in the FAO/WHO JMPR's evaluation (JMPR 2016), studies on both glyphosate and its formulation products were evaluated, and for the most part, major differences were not seen. For example, of the *in vivo* studies of genotoxicity in mammals by the oral route of exposure, less than half were performed with technical glyphosate and more than half were performed with glyphosate formulation products, most of which were different formulations. In the vast majority of the studies, negative results were seen, both with glyphosate and the formulation products. However, in some cases involving other model systems or assays, components of glyphosate formulations have been reported to exhibit toxic and genotoxic effects, and the formulation product has been reported to be more toxic than glyphosate itself. Given the complexity of the situation and the varying composition of formulation products, I believe that it is reasonable to conduct the assessment on glyphosate technical itself.

RESPONSE: *No response is necessary.*

QUESTION: Please comment specifically on the three MRL worksheets in Appendix A.

COMMENT: The worksheets seem generally well done and support the establishment of the respective MRL. I think summarizing the data by endpoint in the various tables (Table A-1, A-2 and A-3) is a good way to illustrate the range of results and why a particular study was selected to be the principal study for each MRL. I suggesting highlighting the principal study that was selected in each table. I also believe that the referencing in Appendix A and throughout the Profile could be improved. The EPA citations used often refer to many studies so it is not easy to determine which is the actual study that is being described. Preferably, the citations should refer to the author or authors names followed by "as cited in" the document that was used. However, this may not be feasible given that the EPA masks information about

the studies. For example, I would prefer that the citation for the principal study for the acute MRL in the Table be MRID 44320616 as cited in EPA (2017b) [or preferably Moxon (1996), as identified in the JMPR Monograph]. This would allow the actual study to be identified and make it easier to keep track of the various studies. If the authors' names could be used that would also give the authors credit as well as allow comparisons to be made between the ATSDR Profile and assessments by other authoritative bodies. I realize that including the MRID number in the tables may make them more unwieldy. Perhaps the key information could be contained in a footnote. As another minor point, the doses should be listed in 1 mg increments. The use of decimal points in the doses (e.g. 1,447.5 in Table A-2, 31.45 in Table A-3, etc.) is not particularly informative and makes it more difficult to identify and compare the doses between studies.

RESPONSE: *The critical effect from the principal study for the acute-duration oral MRL is highlighted in green. Green shading was added to the Table A-3 entry for gastrointestinal effects in the principal study (EPA 1991a, 1991b). The citations for the 2-year mouse study EPA (1985a, 1985b, 1086b, 1989, 1991c, 1993, 2015a) were simplified in tables to EPA (2015a). A statement in Section 2.19 was revised to note that selected results from the 2-year mouse study summarized in EPA (2015a) are also available in EPA (1985a, 1985b, 1986b, 1989, 1993). The revised section states: "In one study, groups of CD-1 mice (50/sex/group) were administered technical glyphosate (99.78% purity) for 24 months at doses of 0, 161, 835, or 4,945 mg/kg/day to the males and 0, 195, 968, or 6,069 mg/kg/day to the females (EPA 2015a; selected results also available in EPA 1985a, 1985b, 1986b, 1989, and 1993)." ATSDR uses a specific convention for the organization of references. This convention was followed in the toxicological profile for glyphosate. MRID numbers from each study summary in which they are identified are included in Chapter 8 (References). The doses in the toxicological profile for glyphosate are the exact (non-rounded) doses reported in the EPA study reviews.*

COMMENT: On page A-11 in the section on the intermediate duration MRL, information is included from EPA (2017b) about a study in pregnant rabbits in which a LOAEL of 175 mg/kg was identified with a NOAEL of 100 mg/kg. This study does not appear to be included within Table A-2 and it is not clear why. It does appear to be the study from which the Acute MRL is derived. From my perspective as indicated below, this study appears to be of intermediate duration and if so, should be included here and within Table A-2. If it is deemed to be an acute study, it should either not be included in this section or it should be made clear that it is an acute study from which the Acute MRL was derived.

RESPONSE: *Information regarding the rabbit study in which dosing was during gestation days 8–20 was deleted from the intermediate-duration oral MRL worksheet because it is summarized in the acute-duration oral MRL worksheet where it belongs.*

Proposed use of the same value for glyphosate technical across three durations of exposure (acute, intermediate, and chronic)

QUESTION: Do you agree that the toxicity database supports it?

COMMENT: I think that the use of the same MRL value for all three exposure periods is acceptable and sufficiently health-protective. However, from my perspective, the ATSDR may want to re-examine the acute MRL. In looking at the various studies and endpoints in Figure 2-3, one can see that the effects seen in the principal study (6H) occurred at much lower concentrations than those that occurred in other studies. An examination of the principal study upon which the acute MRL is based (MRID 44320616) shows that it was actually a 22-day study. The pregnant animals were dosed for 12 days and then observed for an additional 10 days. This would seem to me to fit better within the category of an

intermediate duration study. Acute studies typically involve a single dose or short-term exposure followed by a 14-day observation period. If my interpretation is consistent with that of the ATSDR, the study would be an intermediate dose study and another study with a much higher NOAEL would be selected for the Acute MRL. The currently selected study would be used for the intermediate duration MRL with a NOAEL of 100 mg/kg and an MRL value of 1 mg/kg. However, if ATSDR concludes that MRID 44320616 is an acute study, the acute MRL section would remain as written.

RESPONSE: *The dosing period of 12 days is an acute-duration period according to ATSDR's definition of acute (14 days or less). The 10-day posttreatment observation period does not count because the animals were not dosed during this period.*

QUESTION: Do you agree that pharmacokinetics supports it?

COMMENT: Based upon the literature, the elimination of glyphosate occurs quickly. Elimination half-lives in rodents are generally reported to be approximately 5-10 hr (JMPR, 2017; draft Profile). Elimination in humans, primarily among those attempting suicide, is also quick with an apparent elimination half-life of 3.1 hrs (Roberts et al. 2010). Consistent with this, other reports of human poisoning victims indicate that plasma levels of glyphosate drop rapidly from high to undetectable levels within 2-3 days (Talbot et al., 1991; Henderson et al., 2010b). There is no evidence of bioaccumulation, and none would be predicted based on glyphosate's physical and chemical properties (Farmer (2010); draft Profile). Given its toxicokinetic profile, particularly the human data, I believe that it is reasonable for the acute, intermediate and chronic MRL values to be the same. [This assumes that the acute MRL remains unchanged.]

RESPONSE: *No response is necessary.*

Section 2.19 (Cancer)

QUESTION: Considering that ATSDR does not evaluate chemicals as to their actual carcinogenicity, has ATSDR adequately presented all the available data?

COMMENT: The authors of the draft Profile seem to have done a very good job overviewing the epidemoiological data on glyphosate and summarizing the various analyses. They have also included the recent 2017 update of the Agricultural Health Study (Andreotti et al. 2009). A limited number of animal bioassay results are presented, those in which the data is available from previous evaluations conducted by the USEPA. A peer-reviewed review article by Greim et al., (2015) presents the bioassay data from 9 rat and 5 mouse industry-sponsored guideline studies. Some of the included bioassays are not included in the current Profile. Since these are in a peer-reviewed article, these should either be included or an explanation should be provided for not including them.

RESPONSE: *ATSDR utilizes information from primary sources and does not typically use review articles. ATSDR is attempting to retrieve the unpublished studies summarized in Greim et al. (2015), and they will be included in the profile once they are received. ATSDR did include a summary statement regarding the Greim et al. (2015) article with caveats that it is a secondary source.*

COMMENT: There is a published two-year cancer study of the ammonium salt of glyphosate (13.85% solution) that has not been included (Chruscielska et al., 2000). It should either be included or a reason given for its exclusion (quality, low purity, unknown formulation, etc.).

RESPONSE: *Churuscielska K, Graffstein B, Szarapinska-Kwaszewska J, et al. 2000. Glyphosate. Evaluation of chronic activity and possible far-reaching effects. Part 2. Studies on mutagenic activity. Pestycydy 3-4:21-25 was retrieved. Relevant genotoxicity data were added to draft 11 of the profile.*

COMMENT: In Table 12-2, I would recommend that the evaluations by Japan and Canada also be included. Both evaluations were conducted after the IARC evaluation in 2015 and both regulatory groups concluded that glyphosate was unlikely to be a carcinogenic risk. Summaries of both evaluation are available at the URLs listed below.

Canada: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/registration-decision/2017/glyphosate-rvd-2017-01.html.

Japan: https://www.jstage.jst.go.jp/article/foodsafetyfscj/4/3/4_2016014s/_article/-char/en.

RESPONSE: *The Health Canada Re-evaluation Decision for Glyphosate (2017) (https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/pesticides-pest-management/decisions-updates/registration-decision/2017/glyphosate-rvd-2017-01.html) confirms the decision from the 2015 Health Canada report, Proposed Re-evaluation decision. Glyphosate. PRVD2015-01. The information from the 2015 report that glyphosate was unlikely to pose a human cancer risk was added to Table 2-12 and cited to both Health Canada 2015 and Health Canada 2017.*

The Food Safety Commission of Japan document (http://www.fsc.go.jp/english/evaluationreports/agrichemicalsl_e1.data/kya0100622449b_202.pdf) is an English version summary of the evaluation published in Japanese. It is not included in Table 2-12 due to the brevity of conclusions regarding carcinogenicity in the English summary.

QUESTION: Are there any other studies that need included?

COMMENT: Please see the articles or websites described in the above section.

RESPONSE: *See responses to the identified sources above.*

QUESTION: Any further comments that you have will also be appreciated.

COMMENT: The original date of publication for the IARC monograph was in 2015 so I am not sure why the publication date is listed as 2017. Perhaps the 2017 date refers to an online corrected version. The use of the 2017 date seems somewhat misleading to me and does not allow a reader to easily follow the chronology of publications and events.

RESPONSE: *The 2017 date is the date when the IARC Monograph Volume 112 (which contains the review for glyphosate) was published.*

COMMENT: As indicated above, there are several reports of glyphosate elimination in humans. The ATSDR may want to include this information in the Profile as it would seem to be particularly relevant.

RESPONSE: *The following text was added to the beginning of Section 3.1.4.2: "Roberts et al. (2010) estimated a half-life of 3–4 hours for elimination of glyphosate from the blood of patients who had intentionally ingested large amounts of glyphosate-containing herbicide products. In other cases of poisoning victims, plasma glyphosate levels dropped rapidly (within 2–3 days) following the onset of observation (e.g., Talbot et al. 1991)."*

COMMENT: I suggest that the ASTDR consider including information on reactive oxygen species and the newly identified metabolite glyoxylate be included in a mechanism of action section. In addition, I suggest that a statement be included indicating that there are large numbers of unpublished guideline studies on glyphosate and the inclusion or exclusion of these is likely to or may account for the differences in the conclusions reached by IARC and the other regulatory agencies.

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

The following statement was added to the end of section 2.19. In addition, there are large numbers of unpublished guideline studies on glyphosate and the inclusion or exclusion of these may account for the differences in the conclusions reached by these various agencies.

References

Chruscielska K, Brzezinski J, Kita K, Kalhorn D, Kita I, Graffstein B et al. (2000). Glyphosate - Evaluation of chronic activity and possible far-reaching effects. Part 1. Studies on chronic toxicity. Pestycydy (Warsaw). 3–4:11–20.

Farmer (2010) Inhibitors of Aromatic Acid Synthesis, in Krieger (ed) Hayes' Handbook of Pesticide Toxicology, Vol. 2, 3rd Edition. pp. 1967-1972.

RESPONSE: *Farmer (2010) is a review article; relevant information from this review is already summarized in the toxicological profile. Chruscielska K, Graffstein B, Szarapinska-Kwaszewska J, et al. 2000. Glyphosate. Evaluation of chronic activity and possible far-reaching effects. Part 2. Studies on mutagenic activity. Pestycydy 3-4:21-25 was retrieved. Relevant genotoxicity data were added to draft 11 of the profile.*

Greim H, Saltmiras D, Mostert V, et al. (2015) Evaluation of carcinogenic potential of the herbicide glyphosate drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. Crit Rev Toxicol 45(3):185-208.

Roberts DM, Buckley NA, Mohamed F, Eddleston M, Goldstein DA, Mehrsheikh A, Bleeke MS, Dawson AH. A prospective observational study of the clinical toxicology of glyphosate-containing herbicides in adults with acute self-poisoning. Clin Toxicol (Phila). 2010 Feb;48(2):129-36.

RESPONSE: *These articles are already cited in the ATSDR Toxicological Profile for Glyphosate.*

JMPR (2016) Pesticides residues in food 2016. Special session of the Joint FAO/WHO meeting on pesticide residues. FAO plant production and protection paper. Food and Agriculture Organization of the United Nations, World Health Organization. http://www.fao.org/3/a-i5693e.pdf.

RESPONSE: *This document is already cited in the ATSDR Toxicological Profile for Glyphosate (as FAO and WHO 2016).*

Henderson, A. M.; Gervais, J. A.; Luukinen, B.; Buhl, K.; Stone, D. (2010a) Glyphosate General Fact Sheet; National Pesticide Information Center, Oregon State University Extension Services. http://npic.orst.edu/factsheets/glyphogen.html.

Henderson, A. M.; Gervais, J. A.; Luukinen, B.; Buhl, K.; Stone, D. (2010b) Glyphosate Technical Fact Sheet; National Pesticide Information Center, Oregon State University Extension Services. http://npic.orst.edu/factsheets/archive/glyphotech.html.

RESPONSE: *These fact sheets do not provide primary study results. Information in these fact sheets that is relevant to the ATSDR Toxicological Profile for Glyphosate is already presented in the profile.*

Comments Provided by Peer Reviewer #2

Glyphosate Technical MRLs

QUESTION: Do you agree that exposure to glyphosate technical is possible?

COMMENT: Yes, it may be possible. In the case of inert ingredients, they may have a shorter half-life in the environment than glyphosate salt or, at some point, they could dissociate from glyphosate formulation, in which case the glyphosate salt itself will be the major font of exposure.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree that ingredients and concentrations in glyphosate-based formulations differ too much to assess?

COMMENT: In the Pesticide Database (PAN 2009), in which a hundred and two glyphosate based pesticed products are registered, some of them had their registration status cancelled. In section 5.2.1, pages 115 and 116 present some additives, inert ingredients, and surfactants commonly used in glyphosate formulations. For example, we have one surfactant, four additives and three other active ingredients, totalizing eight possible components for the glyphosate formulations, which still may vary in the final proportion of the commercial formulation.

In fact, the factorial combination of all these ingredients and their used quantities in the formulations potentially produces a large number of groups to be tested individually. It could be more appropriate perhaps, to use more simple tests to evaluate the mixture toxicity for these commercial formulations, such as in silico analysis, than animal experimentation. I agree that assessing the potential toxicity of commercial formulations with the same approach used for technical glyphosate is very complicated. However, I suggest including other analysis, such as silico prediction of toxicity, to assess the potential toxicity of the commercial formulations.

RESPONSE: *ATSDR uses available human and animal data to inform the public of substance-related health effects from exposure. Regarding use of predictive measures of toxicity for glyphosate formulations, it would seem necessary to evaluate the toxicity of each component of a mixture prior to using alternative approaches to predict the toxicity of glyphosate formulations. ATSDR will consider additional information when, and if such information becomes available.*

QUESTION: Please comment specifically on the three MRL worksheets in Appendix A.

COMMENT: In Appendix A, there is a compilation of the minimal risk level worksheets for the noncancer health effects over a specified route and duration of exposure. Only the data from technical glyphosate experiments is included. The first three worksheets refer to the inhalation route in acute, intermediate and chronic duration, and this is insufficient data for the derivation of these MRLs. The next three MRLs present the data provided from acute, intermediate and chronic duration for oral exposure. MRLs were based on the NOAELs and adjusted for a total uncertainty factor of 100, considering that humans are more sensitive to toxic effects than laboratory animals. The provisional MRL calculated for intermediate exposure is twice higher than that observed in the acute and chronic duration MRLs. This

parameter was adjusted for the same MRLs observed for acute and chronic-duration. MRLs for acute, intermediate and chronic-duration are the same (1 mg/kg/day).

RESPONSE: *No response is necessary.*

Proposed use of the same value for glyphosate technical across three durations of exposure (acute, intermediate, and chronic)

QUESTION: Do you agree that the toxicity database supports it?

COMMENT: Yes, I agree. According to the toxicity database, the oral/acute-duration MRL was derived from gastrointestinal effects. Subsequently, in the database for the oral/intermediate toxicity, the gastrointestinal effects are still observed, despite the fact that the range of the doses are different from those used in the acute experiments and consequently, NOAEL and LOAEL are higher than could be expected by derived acute MRL. In the oral/chronic-duration, the inflammation of gastric squamous mucosa is observed and could suggest a more persistent effect in the gastrointestinal tract, supporting the chronicity of the exposure.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree that pharmacokinetics supports it?

COMMENT: Yes, I agree. As presented in Chapter 3, after oral exposure the higher amount of glyphosate is observed in the small intestine and the major route of elimination in this type of exposure, is by feces (57-59%). Therefore, since the glyphosate remains in higher amounts in the gastrointestinal tract it could help to explain the observed effects in the experiments.

RESPONSE: *No response is necessary.*

Section 2.19 (Cancer)

QUESTION: Considering that ATSDR does not evaluate chemicals as to their actual carcinogenicity, has ATSDR adequately presented all the available data?

COMMENT: Yes, the data is presented adequately. In this new version of the cancer section, the reading and the data interpretation are clearer.

RESPONSE: *No response is necessary.*

QUESTION: Are there any other studies that need included?

COMMENT: The criteria of inclusion/exclusion of experiments in this document was the same in all sections. I do not consider the inclusion of additional studies.

RESPONSE: *No response is necessary.*

QUESTION: Any further comments that you have will also be appreciated.

COMMENT: The Toxicological Profile of Glyphosate is the most important document to be released in the field of Toxicology, with direct consequences in agriculture, public health and environmental toxicology. Several aspects are addressed in this document, and the difficulty in selecting appropriate studies to support the database is notable. There is a lengthy discussion between academic and non-academic groups regarding the toxic effects of glyphosate, such as its carcinogenic potential. However, there is still no sufficient available data to support this hypothesis at the moment, and studies are being performed to clarify and properly address this potential toxic effect. This century's recent demand is the development of even safer chemicals and technologies to reduce the damages to human and environmental health. In this sense, this document will bring full and deep information on glyphosate to the academic and non-academic communities to positively contribute to this discussion.

RESPONSE: *No response is necessary.*

Comments provided by Peer Reviewer #3:

Glyphosate Technical MRLs

QUESTION: Do you agree that exposure to glyphosate technical is possible?

COMMENT: If the question refers to if exposure to glyphosate technical alone is possible, while this is a possibility for human beings and thus there is merit in evaluating the toxic effects of glyphosate technical, it is an incomplete inquiry as the vast majority of human exposures to glyphosate are through formulations. As stated in this report, the majority of human exposure to glyphosate is through formulations registered for use in agricultural (food sources containing glyphosate residues) and residential environments. As also noted in the report, such formulations contain wide variations in glyphosate content, including adjuvants and surfactants, which themselves can contribute to the toxicity of glyphosate formulations.

The report states that 'No MRLs were derived for glyphosate formulations due to the wide variation in glyphosate content and surfactants used in various glyphosate formulations…' That surfactants and other adjuvants in formulations can contribute to the toxicity of glyphosate exposure, and that this is the primary route of glyphosate exposure for humans, indicates that focusing only on glyphosate technical MRLs is a shortfall of the report. It's not known to this reviewer if there are other technical reports which do examine MRLs of the common formulations. If not, this merits research.

RESPONSE: *MRLs were not developed for specific glyphosate-containing products due to a lack of sufficient health effects data. If sufficient information were available to assess whether the toxicity of individual glyphosate-containing formulations is similar across the formulations, it might be feasible to derive MRLs for the products, at least for those products to which pesticide applicators and the general population are most likely to be exposed. Previous peer reviewers determined, and ATSDR agrees, that an MRL for glyphosate technical would provide useful information to serve as guidance for assessments.*

QUESTION: Do you agree that ingredients and concentrations in glyphosate-based formulations differ too much to assess?

COMMENT: I don't agree. As noted above, the most common route for human exposure to glyphosate is through formulations, and it is known that formulations themselves can add to toxicity. Thus, despite the significant costs of conducting studies of formulations to assess exposure and outcomes in humans, these should be systematically conducted to determine MRLs for the more common residential and agricultural formulations. Some insight into the degree to which this would be promising to assess could be gained by identifying outcomes of animal feeding studies (of comparable design and duration and exposure) of glyphosate technical alone and of common glyphosate formulations such as Roundup. If the latter findings appeared more toxic, then confidence could be gained to establish MRLs for those formulations suggested.

RESPONSE: *Limited animal data are available regarding the effects of exposure to glyphosate-containing formulations. Data available to ATSDR were included in the Toxicological Profile for Glyphosate. However, at this time, the data are too limited to serve as basis for MRL derivation. Additional studies are needed in order to consider derivation of MRLs for particular glyphosate formulations.*

QUESTION: Please comment specifically on the three MRL worksheets in Appendix A.

COMMENT: See comments below regarding Appendix A and the three tables.

RESPONSE: *No response is necessary.*

Proposed use of the same value for glyphosate technical across three durations of exposure (acute, intermediate, and chronic)

General Comments

COMMENT: Based on data presented in Tables A-1, A-2, and A-3, the acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) MRL levels for oral routes of exposure were set at 1 mg/kg/day. For most humans, the given the oral exposure through foods, the most relevant considerations are the intermediate and especially chronic exposure MRL levels. While based on the data in the tables the levels seem reasonable, more broadly, the idea of a safe, acceptable level of compounds such as glyphosate remains controversial. Such set levels vary markedly depending on the country. The acceptable daily intake of glyphosate in the EU, for example, is 0.3 mg/kg/day while in the US it is higher at 1.75 mg/kg/day. Studies by Mesnage et al. examining the liver transcriptome profile following dosage of 50 ng/L of glyphosate/day (via Roundup ingestion) showed hepatotoxicity (Environ Health. 2015;14:70).

RESPONSE: *ATSDR considers that available data support the oral MRL value of 1 mg/kg/day for glyphosate technical. This MRL will be revisited as additional data become available for glyphosate. The identified study of Mesnage et al. (2015) was retrieved. These investigators claim that 4 ng glyphosate/kg body weight/day (from a roundup formulation) received by rats from the drinking water in a 2-year study (Serafini et al. 2014) resulted in anatomorphological and blood/urine changes indicative of liver and kidney effects. The 2-year study had previously been published and subsequently retracted. Mesnage et al. (2015) performed a study to examine the basis for the effects reported by Serafini et al. (2014). No other groups of investigators have observed glyphosate-related effects on liver or kidney of experimental animals at dose levels orders of magnitude higher than those employed by Serafini and coworkers. Therefore, their results are not included in this ATSDR Toxicological Profile for Glyphosate.*

COMMENT: Note on Page A-9 there seems to be an error in text above Table A-2. It reads "The provisional chronic-duration oral MRL of 1 mg/kg/day…", but this should read "acute-duration".

RESPONSE: *The statement in question is correct as stated. The provisional chronic-duration oral MRL of 1 mg/kg/day was adopted as the provisional intermediate-duration oral MRL, although it is the same value as the provisional acute-duration oral MRL.*

COMMENT: Note, it would help facilitate review of the data if the durations of each of the studies was included in Table A-3.

RESPONSE: *The studies in Table A-3 are all of chronic duration (365 days or more). More specific duration data do not appear necessary.*

QUESTION: Do you agree that the toxicity database supports it?

COMMENT: Yes, based on the data available in the Tables.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree that pharmacokinetics supports it?

COMMENT: These was no specific PK / PD data to review so the intention of this question is not clear. ?? The report notes that "Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age", which is related to the PK / PD question, yet there are no studies specifically examining this issue. This gap in the literature merits clinical studies to be conducted.

RESPONSE: *The following statement was added to Section 6.2 (Children's Susceptibility): "As additional data become available, age-related issues regarding susceptibility to glyphosate toxicity should be evaluated."*

Section 2.19 (Cancer)

QUESTION: Considering that ATSDR does not evaluate chemicals as to their actual carcinogenicity, has ATSDR adequately presented all the available data?

COMMENT: The report reviews a broad range of human and animal cancer-relevant studies. It's not clear why these data are included in the report since ATSDR does not consider possible cancer effects in determine MRLs. In response to the question, ATSDR has presented a representative body of that literature, yet in the end there is no specific position taken, other than to state in Table 2-12 the positions that other national and international private and governmental groups have taken on this question of possible carcinogenicity.

RESPONSE: *ATSDR Toxicological Profiles include results from studies that evaluate cancer endpoints, although MRLs are derived for noncancer effects. ATSDR does not take a position on the carcinogenicity of a substance, but rather defers to agencies and institutions responsible for carcinogenicity evaluations.*

QUESTION: Are there any other studies that need included?

COMMENT: There are two new carcinogenicity publications on this topic that I didn't see in the report:

J Natl Cancer Inst. 2018 May 1;110(5):446-447. doi: 10.1093/jnci/djx247. Glyphosate Use and Cancer Incidence in the Agricultural Health Study: An Epidemiologic Perspective. Ward EM[1,2].

J Natl Cancer Inst. 2018 May 1;110(5):509-516. doi: 10.1093/jnci/djx233. Glyphosate Use and Cancer Incidence in the Agricultural Health Study. Andreotti G[1], Koutros S[1], Hofmann JN[1], Sandler DP[2], Lubin JH[3], Lynch CF[4,5], Lerro CC[1], De Roos AJ[6], Parks CG[2], Alavanja MC[7], Silverman DT[1], Beane Freeman LE[1].

RESPONSE: *The report of Andreotti et al. (2018) is cited in the ATSDR Toxicological Profile for Glyphosate as: Andreotti et al. (2017) (available as epub ahead of print). The citation has been updated*

to reflect the publication date of 2018. The report of Ward (2018) summarizes the findings of Andreotti et al. (2018) and does not contain additional information relevant to the Toxicological Profile for Glyphosate.

QUESTION: Any further comments that you have will also be appreciated.

COMMENT: No further comments provided.

RESPONSE: *No response is necessary.*

Comments Provided by Peer Reviewer #4

General Comments

COMMENT: Human exposure to glyphosate (GPA) technical is quite likely via food, since the herbicide is used widely on crops. Persons who manufacture, formulate, and spray the chemical have the potential for substantially greater expose than the general public, as do people proximate to the spraying operations.

GPA and surfactant concentrations in various formulations vary so much that it is difficult-to-impossible to extrapolate results from one toxicity, or carcinogenicity study to another. It would be very useful, however, if any correlation could be established between GPA content/dose and the magnitude of specific adverse effect(s). Has this been attempted by the EPA using the proprietary GPA data available to the agency? Is there sufficient detail in such study reports to estimate GPA dosage levels and durations? It would also be helpful to examine any studies of formulations in which the GPA dose were held constant and the surfactant concentration varied.

RESPONSE: *Comparative health effects data for various glyphosate formulations are not presently available. When such data become available, ATSDR will review the data and make appropriate revisions.*

COMMENT: An overview or summation of the process by which 1 mg/kg/day was selected for the acute, intermediate, and chronic MRLs should be included in Appendix A. It was necessary to read and compare the content of the three worksheets several times, in order to understand what was done and why it was done. There is a considerable amount of detail about different experimental protocols and results that must be sorted out, before the reader can understand the rationale and logic the chemical manager used in arriving at a MRL for each duration of exposure.

Selection of the same oral exposure level (i.e. 1 mg/kg/day) is reasonable, although I am not sure fully supported by the available database. Part of my problem is ATSDR's definition of an acute exposure as lasting 1 to 14 days. I still think of an acute exposure as being a single exposure of varying duration. It is not clear when the rabbits gavaged daily with GPA from GD 8-20 initially developed diarrhea (EPA, 2017b). The NOAEL for pregnant rats dosed once was reported to be 1,000 mg/kg. Application of an uncertainty factor of 100 would result in an acute MRL of 10 mg/kg/day. I support the intermediate-duration MRL of 2 mg/kg/day. This number is based upon both GI effects and cellular changes in the salivary glands of rats. I would not dismiss the morphological changes due to "uncertainty regarding the adversity of the effect." Basophilia at the light microscopic level is typically evidence of cellular proliferation. Hypertrophy and proliferation, even if due to irritation by GPA, warrant some concern due to the potential carcinogenicity of GPA. I believe the chronic MRL of 1 mg/kg/day is reasonable and supported by the GI histopathology data.

The proposed acute, intermediate, and chronic MRLs are reasonable in light of existing pharmacokinetic data. GPA is not deposited in any particular organ or tissue, so there is not concern about an as-of-yet unidentified target organ. GPA is minimally metabolized, so there is not a concern about a potentially cytotoxic or mutagenic metabolite. GPA has a short half-life, and therefore should not accumulate and produce more serious effects upon repeated exposure.

RESPONSE: *The various duration MRLs (acute, intermediate, chronic) are independently derived. In Appendix A, an MRL worksheet is presented for each route and duration. The MRL Summary near the*

top of each MRL worksheet contains a statement regarding the basis and methodology applied to the MRL derivation for that exposure route and duration. In the case of glyphosate, the acute- and chronic-duration oral MRLs happen to be the same value, although they were derived from completely different sets of data. The chronic-duration oral MRL was adopted as the intermediate-duration oral MRL; explanatory text for this adoption is included in the intermediate-duration oral MRL worksheet.

ATSDR has defined acute-duration exposure as exposure that can be repeated or continuous for up to 14 days. A 14-day period of exposure at a particular exposure level might be expected to result in effects that would not be elicited by a single exposure at the same exposure level. In many cases, an acute-duration MRL will be based on repeated or continuous exposure over multiple days rather than a single exposure.

COMMENT: The presentation of carcinogenicity study protocols and data was detailed and comprehensive. ATSDR staff did a particularly nice job describing epidemiological studies and their findings.

I do not know of any additional carcinogenicity studies that should be included in the Toxicological Profile. ATSDR should, however, consider presenting an overview of the important controversy about IARC's designation of GPA as a probable human carcinogen. Portier et al (2016), in their support of the IARC action, contend that there is limited evidence of carcinogenicity in humans, sufficient evidence of carcinogenicity in animals, and strong evidence of two carcinogenicity mechanisms. Tarazona et al. (2017) present a more balanced narrative, in which they describe difference between the IARC and European Food Safety Authority assessments.

RESPONSE: *ATSDR does not take a position on the carcinogenicity of a substance, but rather defers to agencies and institutions responsible for carcinogenicity evaluations. ATSDR has summarized the evaluations of other entities, but has not entered into discussions regarding differences between these entities and possible bases for the differences. Both Portier et al. (2016) and Tarazona et al. (2017) were cited in Section 2.19.*