DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR ALDRIN/DIELDRIN

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

January 2021

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Comments provided by Peer Reviewer #1

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1

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

COMMENT 1: I agree with the health effects noted in the profile.

RESPONSE: *No response needed.*

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

COMMENT 2: I agree that the effects noted in animals are likely to be of concern to exposed humans. While mainly central nervous system excitation has been noted following acute and chronic exposure, the effects observed in animals (body weight changes, hepatic, neurological, reproductive, and developmental effects) are toxicities that can occur in humans.

RESPONSE: *No response needed.*

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

COMMENT 3: The exposure conditions for animal studies were adequately described in this section. However, human exposure data was not provided, perhaps this is due to a lack of information on human exposures. If this is correct, then perhaps a statement describing that exposure information is lacking for human exposures could be added to this section4

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

In general, the epidemiological data are lacking dose-response information.

Specific Comments on Chapter 1

COMMENT 4*:* p13, line 7 – the bullet for body weight effects in included (aldrin), however, there is not a paragraph describing the effects in the section below. There are paragraphs for all other bulleted effects listed in the text.

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

Body Weight Effects. Decreases in body weight gain have been observed in rats and dogs exposed to aldrin in the diet for intermediate or chronic durations (Deichmann et al. 1970; NCI 1978a; Treon et al. 1955); weight loss has also been observed in dogs chronically exposed to aldrin (Fitzhugh et al. 1964).

Minimal Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation? Please explain.

COMMENT 5: I agree:
Aldrin: acute animal data are limited and lack of exposure concentration-response and purity data, precluding the derivation of an acute-duration inhalation MRL for aldrin. No intermediate intermediate or chronic inhalation exposure data is available for aldrin. For oral exposure, I agree that an intermediate MRL could not be derived since the lowest level tested (0.26 mg/kg/day in the 3-generation study) represents a serious LOAEL (increased pup mortality) in the absence of an identified NOAEL. While hepatic changes were seen in Carworth rats (0.53 mg/kg NOAEL and 2.6 mg/kg LOAEL), these values are higher than seen for adverse reproductive outcomes as noted above.

Dieldrin: No acute-, intermediate-, or chronic-duration inhalation data were located for experimental animals. Therefore, inhalation MRL's cannot be derived. For oral exposure, I agree with not deriving an acute MRL since no other supporting data exists for an immune response identified in a single study at 0.09 mg/kg/day, further the immune system has not been identified as a sensitive target of dieldrin toxicity in humans

RESPONSE: *No response needed.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 6: Yes, I agree with the MRLs that have been proposed for aldrin and dieldrin.
Aldrin: acute oral MRL is based on a LOAEL of 2 mg/kg/day for neurobehavioral effects (increased electroconvulsive shock threshold, the study did not identify a NOAEL) in offspring of maternal mice administered aldrin by gavage during the third trimester of pregnancy (Al-Hachim 1971). Three additional studies identified 2mg/kg/day as a LOAEL. I also agree with the uncertainty factors applied: 10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability.

Aldrin: chronic oral MRL was based on a LOAEL of 0.037 mg/kg/day for increased liver weight and hepatic histological alterations (enlarged centrilobular hepatocytes with cytoplasmic oxyphilia, and peripheral migration of basophilic granules) in rats receiving aldrin from the food for 2 years (Fitzhugh et al. 1964). While I agree with the selection of this study and endpoint, additional information should be included in this section to explain why the study of Deichmann et al., 1970 was not selected. This study used Osborne Mendel rats with exposure for a longer duration (31 months) and identified hepatic changes in exposed male rats at lower doses (and identified a NOAEL) than in the Fitzhugh et al study. I agree with the uncertainty factors applied in the Fitzhugh study - 10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability.

Dieldrin: intermediate oral MRL is based on a study with NOAEL of 0.01 mg/kg/day and a LOAEL of 0.1 mg/kg/day for impaired task learning in squirrel monkeys administered dieldrin orally for 55 days (Smith et al. 1976). As a NAOEL was identified in this study, I agree with the composite uncertainty factor of 100 that was applied – 10 for human variability and 10 for extrapolation from animals to humans.

Dieldrin: chronic oral MRL is based on a NOAEL of 0.005 mg/kg/day and LOAEL of 0.05 mg/kg/day for increased liver weight in female rats administered dieldrin orally for 2 years (Walker et al. 1969). I agree with the composite uncertainty factor of 100 that was applied – 10 for human variability and 10 for extrapolation from animals to humans.

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

   Comments on the use of uncertainty factors are included in my summary, above.

RESPONSE: *Derivation of MRLs are discussed in detail in Appendix A of the profile. Section 1.3 is limited to a table presentation of the MRL values without discussion on how the values are derived; a footnote in Table 1-1 refers the reader to Appendix A for additional information. As discussed in the aldrin chronic oral MRL worksheet in Appendix A, the Fitzhugh et al. (1964) study was selected as the critical study because it identified the lowest LOAEL (0.037 mg/kg/day). This LOAEL is lower than the NOAEL of 1.4 mg/kg/day identified in the Deichmann et al. (1970) study*

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

COMMENT 7: P203, lines 15-16. It might be useful to specify whether the acute, intermediate, chronic time durations noted are for animals.

As noted above, for the chronic MRL for aldrin, information on why the Diechmann et al study was not selected should be included in this section

RESPONSE: *The acute, intermediate, and chronic durations are not species-specific. The durations—1–14 days for acute, 15–364 days for intermediate, and ≥365 days for chronic—are defined in Section 2.1 and in the introduction to Appendix A, starting on page A-1.*

Please see the Response to Comment 6 on why the Deichmann et al. (1970) was not selected as the basis for the chronic-duration MRL.

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature? If not, please suggest appropriate changes.

COMMENT 8: I agree that the conclusion made concerning the health effects of aldrin and dieldrin adequately reflect the published literature.

RESPONSE: *No response needed.*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT 9: Yes, I agree that the available human studies were presented in the text. Study limitations and confounding were sufficiently presented and were not excessive in length.

RESPONSE: *No response needed.*

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT 10: Yes, I agree that the adequately designed animal studies were presented in the text. In cases where the studies had limitations (small group size, limited dosing), they were adequately described in this section. Studies that were selected to derive MRLs represented well designed studies.

RESPONSE: *No response needed.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT 11: Yes, the animal species were appropriate to detect the toxicological endpoints in each study.

RESPONSE: *No response needed.*

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

COMMENT 12: Yes, I agree that attention was given to dose response relationships for aldrin and dieldrin, for both animal and human data. For most human studies, dose-response data was not available, and this was adequately noted in the document.

RESPONSE: *No response needed.*

QUESTION: Are you aware of any studies that are not included in the profile that 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.

COMMENT 13: I am unaware of any additional studies that are related to the toxicity of aldrin or dieldrin that should be included in the profile. The literature review and search strategy was very thorough.

RESPONSE: *No response needed.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

COMMENT 14: I am unaware of any additional studies that would be relevant to the derivation of an MRL for aldrin or dieldrin that should be included in the profile.

RESPONSE: *No response needed.*

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

COMMENT 15: The appropriate NOAELs and LOAELs were identified for each study and were clearly shown I the text, and LSE tables and figures.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT 16: While it is acknowledged that the designation of “serious” and “less serious” when using LOAELs, I agree the the designations used in the LSE tables. As described in this chapter, "Serious" effects were listed for LOAELs that evoke failure in a biological system and can lead to morbidity or mortality whereas, "Less serious" effects were ascribed in instances where a LOAEL was for effects that were not expected to cause significant dysfunction or death, or whose significance to the organism was not clear.

RESPONSE: *No response needed.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT 17: Yes, to my knowledge, all possible mechanisms of action for aldrin and dieldrin were included in this chapter of the profile.

RESPONSE: *No response needed.*

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.

COMMENT 18: I agree that the conclusions presented for aldrin and dieldrin were appropriate

RESPONSE: *No response needed.*

Specific Comments on Chapter 2

COMMENT 19: P20 lines 25-26 – indicates that developmental and body weight changes are also sensitive endpoints for aldrin, however, P20, lines 6-8 indicate that developmental effects occurred in both aldrin and dieldrin exposed animals. Please clarify this section. Also, no summary information is provided for body weight changes for aldrin in this section.

RESPONSE: *The text in Section 2.1 summarizing the health effects has been revised and a summary of the body weight effects was added.*

Animal studies that employed the oral exposure route suggest that hepatic, neurological, reproductive, and developmental endpoints are most sensitive to aldrin and dieldrin toxicity. Body weight is also a sensitive endpoint for aldrin toxicity.

Body weight effects. Body weight effects represent a presumed health effect endpoint for humans exposed to aldrin. Decreases in body weight gain and weight loss have been reported in rats and dogs orally exposed to aldrin.

COMMENT 20: Tables 2-1 & 2-2: It is unclear why multiple entries are included for the same study – for example, Jamaluddin and Poddar 2001b – 3 entries are included in the table (#3-5) each providing different information. As only one reference in included in the literature cited, it is presumed these are from the same study. Can these data be consolidated (additional lines per section)? If not, as it appears that each entry is describing a specific adverse toxicity observed, perhaps that information could be made clear before the reader examines the table.

RESPONSE: *When there are multiple experiments published in the same paper, they are treated as separate entries in the LSE tables and figures.*

COMMENT 21: P62, lines 28-30. It is unclear what study the second sentence is referencing "Hyaline droplet degeneration was observed in the livers of dogs that ingested 0.12–0.25 mg aldrin/kg/day for 15.7 months (Treon et al. 1955). Similar effects were not observed in dogs that ingested 0.14–0.26 mg dieldrin/kg/day over the same period. "

RESPONSE: *Both statements referring to hyaline droplet degeneration were deleted from Section 2.9. Upon re-evaluation of the Treon et al. (1955) studies, it was determined that the small number of animals tested limited the interpretation of this finding.*

COMMENT 22: P 83, lines 24 and 25. "Thorpe and Walker (1973) reported increases in both hepatocellular adenomas (Type A tumors) and hepatocellular carcinomas (Type B tumors) in CF1 mice treated for up to 2 years. " Is reference to "TypeA or B tumors" needed, as the descriptors adenoma and carcinoma have been included.

RESPONSE: *In Section 2.19, the reference to Type A and Type B tumors was deleted:*

Thorpe and Walker (1973) reported increases in both hepatocellular adenomas and hepatocellular carcinomas in CF1 mice treated for up to 2 years.

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

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

COMMENT 23: In general, I agree that there was adequate discussion of the absorption, distribution, metabolism and elimination of aldrin/dieldrin. A couple instances where the document might be more clear are provided below.

P 98, lines 5-7 – there is a wide dose range (0.0002 – 2.5 mg/kg/day) and a large range listed for the steady state for dieldrin (4–39 weeks). Although it was noted that equilibrium was reached earlier in rats receiving higher doses of dieldrin, it might be useful to clarify this section.
P99, lines 11-12 – please confirm the sentence referencing P448 – this is older terminology. Also, this section refers to the enzyme "epoxide hydratase" – the more common name for this enzyme is epoxide hydrolase.

RESPONSE: *Regarding the statement in Section 3.1.2 on time to steady state in rats administered dieldrin, ATSDR has re-evaluated the data and the sentence has been revised:*

> In rats receiving 0.002–0.10 mg/kg/day dieldrin from the diet, steady state was reached by 6 weeks (Davison 1973); time to steady state was similar at the tested dose levels.

Regarding the use of older terminology in Section 3.1.3, the text has been revised to delete cytochrome P-448 and epoxide hydratase was replaced with epoxide hydrolase:

> Thus, cytochrome P-450 seems to be involved in epoxidation.
>
> Dieldrin is also metabolized by epoxide hydrolase to form 6,7-*trans*-dihydroxydihydroaldrin, which was originally isolated and identified in rabbits and mice (Korte and Arent 1965) and later found also to form in other animals, including Rhesus monkeys and chimpanzees (Müller et al. 1975).

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

COMMENT 24: Yes, as noted in this section, no published PBPK models are available for aldrin or dieldrin.

RESPONSE: *No response needed.*

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

COMMENT 25: I agree, that section 3.1.6 of the profile provides an adequate description of animal and human toxicokinetics.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

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

COMMENT 26: I am not aware of any other relevant data concerning childrens health or developmental effects that should be included in the profile for aldrin/dieldrin.

RESPONSE: *No response needed.*

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

COMMENT 27: Included within Section 3.2 was a summary of available information on known exposures in the young and occupationally exposed workers, and animal data describing early lifestage exposure conditions. I agree that these represent potentially susceptible populations. I am not aware of any publications concerning other populaitons that might be considered at higher risk for toxicities to aldrin or dieldrin.

RESPONSE: *No response needed.*

Biomarkers of Exposure and Effect

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

COMMENT 28: Yes, I agree that the biomarkers of exposure are specific for aldrin and dieldrin. As the profile notes, aldrin is rapidly metabolized to dieldrin, and therefore, detection of dieldrin in the blood may indicate either recent or past exposure to aldrin or dieldrin.

RESPONSE: *No response needed.*

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

COMMENT 29: No – as discussed in section 3.3.2 in the profile, there are a number of parameters that can be monitored to provide useful information when exposure to aldrin or dieldrin is suspected, however, none of the described effects are specific to aldrin or dieldrin exposure.

RESPONSE: *No response needed.*

Interactions with Other Chemicals

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? Please explain and provide any additional references.

COMMENT 30: As described in section 3.4 of the profile, there is limited information regarding the influence of other chemicals on the toxicity of aldrin and dieldrin. This section adequately described the available data.

RESPONSE: *No response needed.*

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

COMMENT 31: Yes, there have been limited studies conducted to evaluate the potential interaction of other chemicals with aldrin or dieldrin. As noted above, these studies have been adequately described in section 3.4 , which also does provide any mechanistic information. I am not aware of additional studies that could be added to this section.

RESPONSE: *No response needed.*

Chapter 4. Chemical and Physical Information

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

COMMENT 32: To my knowledge, the information provided for the chemical and physical properties of aldrin and dieldrin are correct.

RESPONSE: *No response needed.*

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

COMMENT 33: N/A - I did not locate information on different forms of aldrin or dieldrin in this section

RESPONSE: *No response needed.*

Chapter 5. Potential for Human Exposure

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

COMMENT 34: I am not aware of any additional information in production, import/export, use or disposal of aldrin/dieldrin that should be included in this profile.

RESPONSE: *No response needed.*

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

COMMENT 35: Yes, adequate information on release into the environment and potential routes of human contact is included in chapter 5 of the profile.
P115 – for both aldrin and dieldrin the text lines 6-7 and 16-17 states that "However, the number of sites in which dieldrin has been evaluated is not known." Does this sentence mean that it is not know at how many sites these chemicals have been measured (the concentrations)?
Page 121 – the title for Table 5-2 describes reported releases of Aldrin. Is there a similar table for reported dieldrin releases (or is this table presenting combined data for both aldrin and dieldrin)? Reading

through this section appears that this table may be referring to aldrin and dieldrin releases combined. Clarification would be helpful.

A summary of the available information on the occurrence of aldrin and dieldrin at NPL sites is provided in Table 5-6.

I am not aware of other information that could be included in this section of the profile.

RESPONSE: *Regarding the statement in Section 5.1 on the number of NPL sites in which aldrin and dieldrin have been measured, the Reviewer is correct, the number of NPL sites in which aldrin or dieldrin have been measured is not known.*

Regarding Table 5-2, the data listed in the table are for aldrin. Dieldrin is not on the Toxic Release Inventory chemical list. The text in Section 5.3 was revised to clarify that the data are for aldrin:

> Table 5-2 summarizes the releases of aldrin to the environment as reported to the TRI; dieldrin is not on the TRI chemical list.

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

COMMENT 36: Yes, this chapter of the profile contained an adequate summary of the available information on the transport, partitioning, transformation and degradation of aldrin and dieldrin in all media. I am not aware of any additional data that cen be added to this section of the profile.

RESPONSE: *No response needed.*

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

COMMENT 37: Yes, considerable data monitoring has been collected for aldrin and dieldrin. Chapter 5 of the profile contains a thorough summary of the monitoring of aldrin and dieldrin in air, water and sediment/soil, as well as other media (wildlife, etc). It appears that proper units were used for each medium, and the form of the chemical measured was also included. Further, there appears to be an adequate discussion of the quality of the data. I am not aware of any other studies that should be included in this section.

RESPONSE: *No response needed.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT 38: Yes, chapter 5 of the profile adequately describes sources and pathways of exposure for the general population, those who were occupationally exposed, and other populations with potentially high exposures. In the latter category, children, in general were considered populations with potentially high exposures and included data from children living in a households with an agricultural farmworker and infants consuming breastmilk. In addition, brief mention of individuals with skin conditions and residents living near hazardous waste sites (in which aldrin/dieldrin have been identified) might be considered population that might have high exposures. I agree with the selection of these populations.

RESPONSE: *No response needed.*

Specific Comments on Chapter 5

COMMENT 39: Page 154, Table 5-9. The description of this table indicates that it is desacribing calculated daily intakes for adults, toddlers, and infants. However, the table depicts years across the column header, and age group/gender/ethnicity in the row header. Is this table presented correctly?

RESPONSE: *Table 5-9 in Section 5.7 has been corrected. The correct row headers are adult, infants, toddlers.*

COMMENT 40: Page 155, lines 1-15. This paragraph appears to describe monitoring data and does not specifically refer to a population with potentially high exposure. Should this paragraph be included within this section?

RESPONSE: *The discussion of exposure in children and infants was moved from Section 5.7 to Section 5.6.*

COMMENT 41: Page 155, lines 21-32. These paragraphs seem out of place. Should these paragraphs be moved to other locations earlier within this section, when other similar information was presented?

RESPONSE: *As noted in the Response to Comment 40, the discussion of infant and child exposure has been moved from Section 5.7 to Section 5.6.*

Chapter 6. Adequacy of the Database

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

COMMENT 42: I am not aware of any additional studies that have been performed and would fill in a data gap.

RESPONSE: *No response needed.*

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

COMMENT 43: Page 162, description of developmental effects (lines 22-25). This section describes the lack of human effects, however, the profile has not provided a summary assessment of available animal data or rendered an opinion as to whether a data gap exists. A brief summary should be included in this section of the profile (as it is noted that this is discussed under children susceptibility).

Comparative toxicokinetics was identified as a data gap, page 165 states - "Further studies across several species and via all three exposure routes would be useful in determining similarities and differences between humans and animals." While this may represent a data gap, as aldrin/dieldrin are not longer in use, and their presence is limited to areas around disposal (NPL) sites, it is not likely that the general population would be exposed to dieldrin at levels high enough to cause adverse toxicities, thus I do not feel that studies evaluating toxicokinetics across species is needed.

The potential for Children susceptibility was identified as a data gap. Page 165 notes that "Further studies that evaluate a number of different endpoints in young as well as older organisms would provide valuable information." Further, the only available animal studies conducted in the 1970's have been conflicting with respect to developmental endpoints. As measurable levels of dieldrin exist environmentally and children/developmental exposure may results in adverse events, I agree that animal studies evaluating developmental outcomes following dieldrin exposure would be useful.

Pharmacokinetic differences between children and adults was identified as a data gap, since no data is available. I feel that determining whether early life exposures to dieldrin result in developmental effects is needed first. If it is determined that dieldrin elicits developmental then the PK studies might be useful. I agree that Information regarding stockpile levels of aldrin and dieldrin, and current disposal methods would be useful.

Concerning bioavailability in environmental media, is was noted that information is needed on the absorption of the compounds following ingestion of contaminated drinking water and soils and would be useful for evaluating the importance of various routes of exposure to populations living in the vicinity of hazardous waste sites. While this may be true, perhaps human biomonitoring, including quantitation in children – specifically near hazardous waste sites - would provide a direct measure of exposure (rather than estimates of dietary intake), regardless of the route of exposure – this is noted as a data gap on page 168, lines 17-22, and 24-33.

RESPONSE: *Regarding developmental effects, the following statement was added to Section 6.2-Health Effects:*

> Developmental effects such as increased postnatal mortality and external and skeletal malformations/anomalies have been observed in animal studies.

Regarding the comparative toxicokinetics data need in Section 6.2, the purpose of the data needs section is to identify data gaps; it does not prioritize or recommend which studies should be conducted.

No response is needed to the Reviewer's comment on the Children's Susceptibility data need in Section 6.2.

Regarding the identification of a data need for studies evaluating potential pharmacokinetic differences between children and adults, the purpose of the data needs section is to identify data gaps; it does not prioritize or recommend which studies should be conducted.

The need for studies evaluating bioavailability from environmental media is different from the need for biomonitoring. As noted previously, the purpose of Section 6.2 is to identify data gaps.

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

COMMENT 44: Yes, I agree that the data needs section is presented in a neutral, non-biased manner.

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

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

COMMENT 45: I am not aware of any additional regulations or guidelines for aldrin or dieldrin that should be included in this section.

RESPONSE: *No response needed.*

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

COMMENT 46: I agree that the regulations and guidelines for aldrin/dieldrin that are included in this section are appropriate.

RESPONSE: *No response needed.*

Appendices

COMMENT 47: Appendices A-G were well organized and concise. The overall presentation style in the document and appendices makes the document easy to follow, readable, and contained pertinent information for the various audiences that may read the profile (or subsections within).

RESPONSE: *No response needed.*

Comments provided by Peer Reviewer #2

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1

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

COMMENT 1: Yes

RESPONSE: *No response needed.*

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

COMMENT 2: Yes, likely to be of concern to humans. The writeup nicely makes an argument that species differences in ADME are quantitative, not qualitative.

RESPONSE: *No response needed.*

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

COMMENT 3: Yes, a good description.

RESPONSE: *No response needed.*

Minimal Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation? Please explain.

COMMENT 4: I disagree with not deriving an intermediate oral MRL for Aldrin and an acure oral MRL for dieldrin. Specific comments are in the document itself.

RESPONSE: *See the Responses to specific MRL comments in the Annotated Comments section of this document.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose.

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

COMMENT 5: Yes, I agree with all derived MRLs and their methodology/assumptions. Minor edits are in the document.

RESPONSE: *See the Responses to specific comments in the Annotated Comments section of this document.*

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

COMMENT 6: No comments other than those in the text.

RESPONSE: *See the Responses to specific MRL comments (Comments 87 and 88) in the Annotated Comments section of this document.*

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature? If not, please suggest appropriate changes.

COMMENT 7: Yes, good conclusions.

RESPONSE: *No response needed.*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT 8: Yes, overall this is a good text, some minor suggestions are in the document.

RESPONSE: *See the Responses to specific comments in the Annotated Comments section of this document.*

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT 9: Yes, overall this is a good text, some minor suggestions are in the document.

RESPONSE: *See the Responses to specific comments in the Annotated Comments section of this document.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT 10: Yes.

RESPONSE: *No response needed.*

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

COMMENT 11: Yes. Almost all of the studies listed doses. Where that information may need to be adde, I indicated so in the text.

RESPONSE: *See the Responses to specific comments in the Annotated Comments section of this document.*

QUESTION: Are you aware of any studies that are not included in the profile that 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.

COMMENT 12: There were some suggestions made about cancer studies. I have listed the references that should be considered for addition.

RESPONSE: *ATSDR assumes that the Reviewer is referring to the studies listed in Comment 16. As discussed in the Response to Comment 16, none of the studies were added to the profile.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

COMMENT 13: The studies that should be added are not useful for the MRL derivation.

RESPONSE: *No response needed.*

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

COMMENT 14: The numbers are correct.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT 15: Yes. This is an ATSDR-specific terminology and I defer to the agency staff judgement as they apply these across multiple chemicals. It is a subjective call, but as long as it is applied consistently, it should be good.

RESPONSE: *No response needed.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT 16: I do not believe that the mechanistic evaluation is a strength of this document. The practice of systematic evaluation of the mechanistic evidence for cancer and several other endpoints has been an active area of "collective reasoning" and rapid adoption by various agencies. These are published original examples for 3 health effects and more are in development:

1: Luderer U, Eskenazi B, Hauser R, Korach KS, McHale CM, Moran F, Rieswijk L, Solomon G, Udagawa O, Zhang L, Zlatnik M, Zeise L, Smith MT. Proposed Key Characteristics of Female Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Data in Hazard Assessment. Environ Health Perspect. 2019 Jul;127(7):75001. doi: 10.1289/EHP4971. Epub 2019 Jul 19. PubMed PMID: 31322437; PubMed Central PMCID: PMC6791466.

2: Arzuaga X, Smith MT, Gibbons CF, Skakkebæk NE, Yost EE, Beverly BEJ, Hotchkiss AK, Hauser R, Pagani RL, Schrader SM, Zeise L, Prins GS. Proposed Key Characteristics of Male Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Evidence in Human Health Hazard Assessments. Environ Health Perspect. 2019 Jun;127(6):65001. doi: 10.1289/EHP5045. Epub 2019 Jun 14. PubMed PMID: 31199676; PubMed Central PMCID: PMC6792367.

3: Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K. Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis. Environ Health Perspect. 2016 Jun;124(6):713-21. doi: 10.1289/ehp.1509912. Epub 2015 Nov 24. PubMed PMID: 26600562; PubMed Central PMCID: PMC4892922.
21.

RESPONSE: *ATSDR agrees with the Reviewer on the importance of mechanistic data in evaluating health effect risks. However, there are limited mechanistic data for reproductive endpoints available for aldrin and/or dieldrin, thus precluding ATSDR from using the key characteristics discussed in the Luderer et al. (2019) and Arzuaga et al. (2019) papers as support for considering reproductive effects observed in laboratory animals as relevant human health outcomes. Regarding the Smith et al. (2016) paper, ATSDR does not conduct weight-of-evidence analyses to evaluate the human carcinogenic potential of hazardous substances; the toxicological profile cites the carcinogenicity weight-of-evidence conclusions conducted by the Department of Health and Human Services (HHS), U.S. Environmental Protection Agency (EPA), and International Agency for Research on Cancer (IARC).*

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.

COMMENT 17: Yes, the conclusions for section 2 are appropriate, unless minor edits are suggested in the text.

RESPONSE: *No response needed. See the Annotated Comments section for additional information on how the suggested minor edits were addressed.*

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

Toxicokinetics

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

COMMENT 18: Yes, minor edits are in the text.

RESPONSE: *No response needed. See the Annotated Comments section for additional information on how the suggested minor edits were addressed.*

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

COMMENT 19: None are available.

RESPONSE: *No response needed.*

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

COMMENT 20: I suggested deletion of a section in chapter except for section 3.1.6.

RESPONSE: *See the Response to Comment 79 in the Annotated Comments section.*

Children and Other Populations that are Unusually Susceptible

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

COMMENT 21: None that I am aweare of that haven't been already described.

RESPONSE: *No response needed.*

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

COMMENT 22: Genetic susceptibility references were suggested in the text.

RESPONSE: *The Koutros et al. (2013b) and Høyer et al. (2002) studies were added to Section 3.2:*
Two studies evaluated with polymorphisms and cancer risk. In a study of single nucleotide polymorphisms, Koutros et al. (2013b) found an increased risk of prostate cancer risk among men with aldrin use and two A alleles at rs7679673 in TET2 region. The second study examined mutations in the p53 suppressor gene and breast cancer risk associated with dieldrin exposure (Høyer

et al. 2002). Although no significant alterations in breast cancer risk was associated with this polymorphism, women with 'wild-type' p53 had an increased risk of dying.

Biomarkers of Exposure and Effect

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

COMMENT 23: The text is very detailed. No further additions.

RESPONSE: *No response needed.*

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

COMMENT 24: The text is very detailed. No further additions.

RESPONSE: *No response needed.*

Interactions with Other Chemicals

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? Please explain and provide any additional references.

COMMENT 25: Yes, the information is thorough.

RESPONSE: *No response needed.*

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

COMMENT 26: Yes, the information is thorough.

RESPONSE: *No response needed.*

Chapter 4. Chemical and Physical Information

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

COMMENT 27: Not that I am aware of. Everything looks correct.

RESPONSE: *No response needed.*

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

COMMENT 28: The text is good as is.

RESPONSE: *No response needed.*

Chapter 5. Potential for Human Exposure

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

COMMENT 29: Yes, complete. No further edits.

RESPONSE: *No response needed.*

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

COMMENT 30: The chapter is very thorough and informative. Minor edits only.

RESPONSE: *No response needed.*

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

COMMENT 31: The chapter is very thorough and informative. Minor edits only.

RESPONSE: *No response needed.*

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

COMMENT 32: The chapter is very thorough and informative.

RESPONSE: *No response needed.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT 33: The chapter is very thorough and informative.

RESPONSE: *No response needed.*

Chapter 6. Adequacy of the Database

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

COMMENT 34: Studies were suggested for addition in Chapter 2. If added there, please change information here as well.

RESPONSE: *As noted in the Response to Comment 16, the suggested studies were not added to Chapter 2. However, the following statement was added to Section 6.2, Health Effects, Reproductive:*

> Studies examining the mechanisms of action would be useful in evaluating the human relevance of the reproductive effects observed in laboratory animals.

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

COMMENT 35: I agree.

RESPONSE: *No response needed.*

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

COMMENT 36: Yes, a very balanced text.

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

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

COMMENT 37: ECHA regfulations were suggested in the text.

RESPONSE: *The focus of the regulations and guidelines listed in Table 7-1 are U.S. federal values. Although some non-country specific international guidelines (e.g., IARC, World Health Organization [WHO]) are also included, the inclusion of non-U.S. country-specific values is beyond the scope of this chapter.*

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

COMMENT 38: No.

RESPONSE: *No response needed.*

Appendices

COMMENT 39: Comments were provided (see edits in the document) on:
MRL worksheets (Appendix A)
Literature search framework/query strings (appendices B and C)

RESPONSE: *See the Responses to Comments 86–93 in the Annotated Comment section of this document.*

Annotated Comments

The Reviewer suggested a number of editorial revisions, most of the suggested revisions were made to the profile. Some stylistic changes that were purely arbitrary were not incorporated. Responses to Reviewer comments that were not considered editorial or stylistic are presented below.

COMMENT 40: The Reviewer made the following comment in Section 1.1: Please clarify why both are included in this document. How they are related needs to be explained right away

RESPONSE: *The following sentence was added to Section 1.1:*
Aldrin is readily converted to dieldrin under most environmental conditions and in the body.

COMMENT 41: Referring to the statement in 1.1—Aldrin was first produced in 1948—the Reviewer asked "What about Dieldrin production"

RESPONSE: *The referenced sentence was revised:*
Aldrin was first produced in 1948, and dieldrin was first used in 1950.

COMMENT 42: Referring to the statement in Section 1.1-- However, uses of these pesticides were not canceled by EPA until 1989—the Reviewer commented "Please clarify. The use may be banned, the registration may be not renewed or cancelled, by EPA. I am not sure I have seen "EPA cancels…" announcements." and "IARC Monograph 117 states that "Nonetheless, the industry trade literature revealed that 11 companies in the USA between 1989 and 1999, and 7 companies in the USA in 2016 reported production of aldrin and/or dieldrin (Jorgenson, 2001; Chem Sources, 2016)."

RESPONSE: *The referenced sentence in Section 1.1 is correct, EPA cancelled its allowed uses. As presented in Section 5.2.1, there are still companies that produce aldrin and/or dieldrin.*

COMMENT 43: Referring to the statement in Section 1.1—Low levels of aldrin and dieldrin have been detected in, soil, sediment, surface water, and groundwater, and infrequently in public water supplies—the Reviewer commented "Frequency is not indicated in the first part of this sentence… why mention it here?"

RESPONSE: *The referenced sentence in Section 1.1 was revised:*
Low levels of aldrin and dieldrin have been detected in soil, sediment, surface water, groundwater, and public water supplies.

COMMENT 44: Referring to the sentence in Section 1.1—Dieldrin has been detected in selected food items —the Reviewer commented "Can you be more specific?"

RESPONSE: *The statement in Section 1.1 was revised:*

Dieldrin has been detected in food, such as root crops, dairy products, and meat.

COMMENT 45: Referring to the statement in Section 1.2—Available studies in animals employed oral exposure—the Reviewer made the following comment "Gavage, diet? Please be specific.

RESPONSE: *The referenced statement in Section 1.2 was revised:*

Available studies in animals employed oral exposure (via diet, gavage, or capsule).

COMMENT 46: Referring to the statement in Section 1.2—Body weight and developmental endpoints appear to be sensitive targets of aldrin and/or dieldrin toxicity as well—the Reviewer commented "Both directions of the effect is "toxicologically relevant". Do you mean loss or increase? Please be specific here and below."

RESPONSE: *The purpose of the list that the Reviewer is referencing is to identify critical targets. Specific effects are discussed in the text below the list of endpoints. In the discussion of body weight effects, the profile clearly states that decreases in body weight and weight loss were observed in laboratory animals.*

COMMENT 47: Referring to the statement in Section 1.2—Increased liver weight and histopathologic changes were observed among rats administered aldrin or dieldrin in the diet for up to 2 years at doses as low as 0.016–0.092 mg/kg/day (Fitzhugh et al. 1964; Harr et al. 1970; Walker et al. 1969)—The Reviewer commented "absolute, relative? That makes a difference. Please be precise" *and* "Please state whether there were any differences in the doses at which effects were seen for A vs D"

RSPONSE: *The discussion of hepatic effects in Section 1.2 was revised to specify that increases in relative liver weight were observed and to delete the dose levels:*

Increased relative liver weight and histopathologic changes were observed among rats administered aldrin or dieldrin in the diet for up to 2 years (Fitzhugh et al. 1964; Treon et al. 1951a; Walker et al. 1969).

COMMENT 48: Referring to the statement in Section 1.2—In multi-generation reproduction studies in rodents, administration of aldrin or dieldrin in the diet at doses as low as 0.26–0.56 mg/kg/day resulted in decreased fertility (Keplinger et al. 1970; Treon et al. 1954a)—the Reviewer commented "Well, if the animals are convulsing at comparable or lower doses, they are not going to be mating… So how relevant these effects are? You may need to be more granular with dose overlaps for these effects…"

RESPONSE: *Although there is overlap between the doses resulting in overt neurotoxicity and reproductive toxicity, no neurological signs were reported in the reproductive toxicity studies (Keplinger et al. 1970; Treon et al. 1953b).*

COMMENT 49: Referring to the discussion of developmental effects in Section 1.2, the Reviewer commented "Dose ranges were listed for all effects before this one… please be consistent"

RESPONSE: *The dose ranges were deleted from the discussion of the other health effects:*

> ***Developmental Effects.*** Increased postnatal mortality has been one of the most consistent developmental findings reported for aldrin and dieldrin in animals (Deichmann et al. 1971; Harr et al. 1970; Kitselman 1953; Treon et al. 1954a; Virgo and Bellward 1975). Aldrin or dieldrin exposure during gestation has resulted in some evidence of external malformations or skeletal anomalies in animals (Chernoff et al. 1975; Ottolenghi et al. 1974)..

COMMENT 50: Referring to the discussion of cancer effects in Section 1.2, the Reviewer commented "Dose levels?"

RESPONSE: *As noted in the Response to Comment 49, the dose ranges were deleted from the discussion of the health effects in Section 1.2.*

COMMENT 51: Regarding Figure 2-1, the Reviewer commented "IARC monograph 117 also includes Davis et al 1965 animal study that was positive for cancer endpoint. For human studies, there is also a disconnect with what studies IARC included. You list a far greater number here."

RESPONSE: *Davis (1965) is only available as an internal Food and Drug Administration (FDA) memo that ATSDR was unable to obtain. The results of this study were added to Section 2.19 based on information presented in in Epstein (1975) and IARC (2019):*

> Epstein (1975) also summarized an unpublished study conducted by Davis (1965). In this study an increase in the incidence of benign hepatoma was observed in male and female mice exposed to 1.7 mg/kg/day aldrin in the diet for up to 2 years. As with the Davis and Fitzhugh (1962) study, a partial re-evaluation of the tumors classified as benign hepatomas were re-evaluated as hepatocellular carcinomas (Reuber 1976).

Some of the difference between the number of epidemiological studies cited by IARC (2019) and ATSDR is how the studies are counted; ATSDR counts follow-up studies as separate studies, whereas IARC (2019) groups them together.

COMMENT 52: Referring to Figure 2-2, the Reviewer commented "IARC Monograph 117 lists 16 studies in mice, 6 studies in rats and 1 study in hamster for cancer. You mention only 9 here. While not all cancer studies have observed significant increases, some that are not included here did. For human studies, there is also a major disconnect with what studies IARC included. You list a far greater number here."

RESPONSE: *Figure 2-2 was revised to accurately reflect that 13 dieldrin animal cancer studies are discussed in the profile. The three studies cited by IARC (2019) and not included in the draft profile were Davis (1965), Vesselinovitch et al. (1979), and Cameron and Foster (2009). The Vesselinovitch et al. (1979) study was considered a low-quality study because it lacked a vehicle control group and was not added to the profile. As noted in the Response to Comment 51, the Davis (1965) study is only available as an internal FDA memo and was not available to ATSDR. However, a summary of the study results as discussed by Epstein (1975) was added Section 2.19 (see the Response to Comment 51 for the inserted text). The Cameron and Foster (2009) study was also added to Section 2.19:*

> A study of transgenic mouse model of spontaneous mammary tumor formation found an increase in the total mammary tumor burden in female mice administered 4.5 mg/kg dieldrin via gavage (Cameron and Foster 2009). The dams were exposed 5 days/week for 2 weeks prior to mating,

throughout lactation until weaning; the female offspring were exposed 1 day/week until 9 weeks of age.

As noted in the Response to Comment 51, the difference between the number of epidemiological studies cited by IARC (2019) and ATSDR is due to differences in how follow-up studies are counted.

COMMENT 53: Referring to Table 2-1, the Reviewer commented "Cancer bioassay with significant findings that should be included: Davis et al 1965:"

RESPONSE: *As noted in the Response to Comment 51, the Davis (1965) study was not available for ATSDR to review as it is only available as an internal FDA memo. The results of this study, as reported by Epstein (1975), were added to Section 2.19 (see the Response to Comment 51 for inserted text).*

COMMENT 54: Referring to the summary of the Fitzhugh et al. (1964) study in Table 2-1, the Reviewer commented "This study also examined cancer incidence in both sexes combined and reported elevation in one of the doses where survival was the highest."

RESPONSE: *The increase in tumors (all sites combined) at the lowest aldrin dose tested in the Fitzhugh et al. (1964) study was not added to Table 2-1 because there were no significant alterations in total tumor incidence at higher dose levels. A note was added to Section 2.19:*

It is noted that the Fitzhugh et al. (1964) study found an increase in total tumors at the lowest dose tested (0.037 mg/kg/day), but not at higher doses.

COMMENT 55: Referring to Table 2-2, the Reviewer commented "The Davis et al (1965) study had significant findings for the cancer endpoint. Please see IARC description of the re-analysis of this study. Mouse studies of Ruebner et al., 1984; Tennekes et al, 1979; Vesselinovitch et al 1979; Cameron & Forster 2009; also need to be included for cancer."

RESPONSE: *As noted in Responses to Comments 51 and 52, the Davis et al. (1965) (as reported by Epstein 1975) and Cameron and Foster (2009) studies were added to Section 2.19 (see these Responses for inserted text. The Ruebner et al. (1984) and Tennekes et al. (1979) and studies were also added (see below for inserted text). The Vesselinovitch et al. (1979) study is considered a low-quality study and was not added to the profile.*

An increase in hepatocellular adenomas was also observed in a study of male C3H/He mice exposed for 54 weeks followed by an approximate 1-year recovery period (Ruebner et al. 1984); however, there were no increases in adenomas in a second group exposed for 64 weeks followed by the recovery period.

Increased incidences of hepatocellular carcinomas were reported in male C3H/He, B6C3F1, and C57BL/6J mice treated for up to 85 weeks (Meierhenry et al. 1983) and in male CF1 mice treated for up to 92 weeks (Tennekes et al. 1979, 1981).

COMMENT 56: Referring to the summary of the NCI (1978a) dieldrin rat study in Table 2-2, the Reviewer commented "This study also had a significant cancer finding in adrenal gland in Female rats"

RESPONSE: *Although there was a significant increase in the occurrence of adrenal cortical adenomas and carcinomas in the low-dose female rats, when compared to pooled controls, NCI (1978a) noted*

"Although this tumor was also found in animals treated with aldrin, it is not clearly associated with treatment, because the incidence in the high-dose (2/40) was not significant, and the incidences were not significant when matched, rather than pooled, controls were used for comparison." Thus, ATSDR did not include the increase in the adrenal tumors in Table 2-2. The following statement was added to the dieldrin discussion in Section 2.19:

> NCI (1978a) reported an increase in the incidence of adrenal cortical adenomas and carcinomas in female rats administered 2.2 mg/kg/day aldrin, when compared to the incidence in pooled controls. However, the incidence was not significantly different from concurrent controls and no increase in tumor incidence was observed in females administered 5 mg/kg/day; NCI (1978a) noted that the tumor was not clearly associated with treatment.

COMMENT 57: Referring to the summary of the NCI (1978a) dieldrin mouse study in Table 2-2, the Reviewer commented "This study also reported increases in liver tumors in males."

RESPONSE: *The increase in liver tumors observed in male mice exposed to 0.86 mg/kg/day was added to Table 2-2.*

COMMENT 58: Referring to Section 2.2, the Reviewer commented **"**I find this section difficult to follow because the logic of how the information was arranged is not clear. Please consider sub-headings (Human, animal, exposure route, etc.)"

RESPONSE: *The format of the discussions in Sections 2.2 through 2.19 was divided into three subsections (with subheadings): Epidemiological Studies, Aldrin, and Dieldrin.*

COMMENT 59: Referring to the statement in Section 2.2—A lower than expected overall incidence of mortality was observed in a cohort of 570 workers who had been employed in the manufacture of aldrin, dieldrin, endrin, and/or telodrin at a facility in the Netherlands for at least 1 year between 1954 and 1970 (de Jong 1991)—the Reviewer commented ". These two are mentioned for the first time here. Please add a short description as to why are they included."

RESPONSE: *As noted in the referenced statement, endrin and telodrin were also manufactured at the same facility as aldrin and dieldrin, which is why it was noted in the profile. ATSDR disagrees that a discussion of why they are included is necessary.*

COMMENT 60: Referring to the discussion of the de Jong (1991) study in Section 2.2, the Reviewer commented on the duration of exposure "A range and median are more informative than the mean without standard deviation"

RESPONSE: *The text in Section 2.2 was revised to indicate that the workers were under observation for at least 18 years; it is beyond the scope of the section to include the standard deviation of the exposure duration.*

> Although the workers represented a unique population because they had been under observation for at least 18 years

COMMENT 61: Referring to the discussion of the de Jong (1991) study in Section 2.2, the Reviewer commented on and the number of subjects "How many?"

RESPONSE: *The text in Section 2.2 was revised to delete the statement that the evaluations were limited by small number of subjects. Data are not available to calculate the range or median observation period.*

Although the workers represented a unique population because they had been under observation for at least 18 years, the evaluations are limited by uncertainty regarding exposure levels, and the potential exposure of the subjects to more than one of these pesticides and/or to other chemicals at the chemical manufacturing complex.

COMMENT 62: Referring to the discussion of the Spiotta (1951) case report in Section 2.5, the Reviewer commented "Did the patient survive?"

RESPONSE: *The text in Section 2.5 was revised to indicate that he survived:*

A young man who survived an attempted suicide by consuming approximately 25.6 mg/kg of aldrin had extremely labile blood pressure upon admission to the hospital (Spiotta 1951).

COMMENT 63: Referring to the discussion of the Gupta (1975) study in Section 2.15, the Reviewer commented "Any information on contaminant amounts? If not, please state so"

RESPONSE: *The text in Section 2.15 was revised:*

A small group of persons who consumed wheat mixed with aldrin and lindane over a period of 6–12 months developed a variety of central nervous system symptoms (Gupta 1975); exposure levels were not estimated.

COMMENT 64: Referring to the discussion of the Ditraglia et al. (1981) in Section 2.19, the Reviewer commented "IARC Monograph 117 went even further calling these studies "uninformative""

RESPONSE: *The text in Section 2.15 was revised:*

A major limitation of this cohort is the production of numerous other pesticide compounds at the plant in addition to aldrin and dieldrin, which limits the usefulness of the results.

COMMENT 65: Referring to the discussion of the De Jong et al. (1997) and Swaen et al. (2002) studies in Section 2.19, the Reviewer commented "The IARC monograph differs from these conclusions in stating that "Standardized mortality ratios for cancers of the oesophagus, rectum, liver and biliary tract, and skin were elevated based on small numbers of deaths, but were not statistically significant or systematically related to exposure level." Please check the significance."

RESPONSE: *The text in Section 2.19 was revised to include the findings of the latest follow-up study which did not find significant increase in rectal cancers:*

The latest follow-up of this population (van Amelsvoort et al. 2009) found a nonstatistical increase in rectal cancer in the low exposure group, but no increases in the moderate or high exposure groups.

COMMENT 66: Referring to the discussion of the AHS studies in Section 2.19, the Reviewer commented "The AHS is a major undertaking that needs to be mentioned by name. similar to the studies of two plans above."

RESPONSE: *The following statement was added to the discussion of the AHS studies:*

A number of cohort or case-control studies have used data collected as part of the Agricultural Health Study of pesticide applicators in Iowa and North Carolina to evaluate possible associations between self-reported use of aldrin or dieldrin and risk of non-Hodgkin's lymphoma…

COMMENT 67: Referring to Table 2-3, the Reviewer commented "IARC Monograph 117 separated tables for Aldrin and dieldrin. While it is difficult to completely separate the two, the analyses in many studies were done for A and D separately and have slightly different OR/SMR values. Please either consider separating this into 2 tables or explaining why only 1 table is provided."

RESPONSE: *ATSDR opted to discuss the epidemiological data in one table and to divide the table into two sections: Aldrin and Dieldrin.*

COMMENT 68: Referring to Table 2-4, the Reviewer commented "This study was not included by IARC Vol 117 because it was considered to have not "adequately report their methods"

RESPONSE: *The Mathur et al. (2002) study was deleted from the text and from Table 2-4.*

COMMENT 69: Referring to the discussion of animal studies in Section 2.19, the Reviewer commented "See my comments on the Tables 2-1 and 2-2 for individual studies and additional studies"

RESPONSE: *See Responses to Comments 53 and 55.*

COMMENT 70: Referring to the discussion of the sensitive of mice to aldrin and dieldrin induced hepatocarcinogenicity in Section 2.19, the Reviewer commented "I wouldn't include IARC 2019 as a reference for the "nongenotoxic" statement. That wasn't my interpretation of section 5.4 of the monograph. The monograph working group concluded that "No studies on aldrin were available, and there is *moderate* evidence that dieldrin alters cell proliferation, cell death, or nutrient supply."

I wouldn't actually include this paragraph as is at all. It is a good example of a narrative review that has little structure and doesn't appear to have been based on the systematic literature review. ATSDR should be encouraged a systematic approach based on 10 key characteristics as has been done by IARC for the past 4-5 years. A much more comprehensive and systematic evaluation of different cancer mechanisms is provided in section 5.4 of the IARC monograph. IARC concluded, in fact, that no mechanism has "strong" evidence and that at best oxidative stress, genotoxicity and a few others are "moderate".

RESPONSE: *The text in Section 2.19 was revised to delete IARC (2019) from the string reference:*

A preponderance of evidence from studies in a variety of mammalian species indicates a unique sensitivity of the mouse liver to aldrin- and dieldrin-induced hepatocarcinogenicity; mechanistic studies suggest a nongenotoxic mode of action (Stern 2014; Stevenson et al. 1999; WHO 1989) via promotion of spontaneously initiated (background) liver cells.

COMMENT 71: Referring to the statement—The 14th report on carcinogens (NTP 2016a) does not include evaluation of aldrin or dieldrin—the Reviewer commented "This read like the 14th edition doesn't include. Perhaps best to say that the RoC doesn't include and provide a reference to the most recent edition?"

RESPONSE: *The referenced statement has been replaced with the following two sentences in Section 2.19:*

The Department of Health and Human Services (HHS) has not evaluated the carcinogenicity of aldrin (NTP 2016a).

The HHS has not evaluated the carcinogenicity of dieldrin (NTP 2016a).

COMMENT 72: Referring to the summary of the Dulout et al. (1985) study in Table 2-5, the Reviewer commented "Great Catch! This study was actually missed by IARC vol 117"

RESPONSE: *No response needed.*

COMMENT 73: Referring to Table 2-5, the Reviewer commented "Add the Georgian et al. (1975) and Usha Rani et al. (1980) form IARC 2019."

RESPONSE: *The Georgian (1975) and Usha Rani et al. (1980) studies were added to Table 2-5.*

COMMENT 74: Referring to the summary of the Markaryan (1966) study in Table 2-5, the Reviewer commented "Great Catch! This study was actually missed by IARC vol 117"

RESPONSE: *No response needed.*

COMMENT 75: Referring to the summary of the Epstein et al. (1972) study in Table 2-5, the Reviewer commented "Great Catch! This study was actually missed by IARC vol 117"

RESPONSE: *No response needed.*

COMMENT 76: Referring to the summary of the Rocchi et al. (1980) study in Table 2-6, the Reviewer commented "Great Catch! This study was actually missed by IARC vol 117"

RESPONSE: *No response needed.*

COMMENT 77: Referring to Table 2-7, the Reviewer commented "Add Backowski et al. 1998 study in rats (from IARC 2019 Table 4-3)"

RESPONSE: *The Backowski et al. (1998) study was added to Table 2-7.*

COMMENT 78: Referring to Section 3.1, the Reviewer commented "There is no section on modulation of metabolic enzymes. Some mention is in sections 3.3.2 and 3.4. But perhaps a section should be added earlier in section 3, perhaps after current 3.1.4. Excellent summary is included in IARC 2019 (section 4.1.4 (c)) and is informative to the overall TK."

RESPONSE: *ATSDR does not consider modulation of metabolic enzymes that could result in the altered toxicity of another chemical to be a toxicokinetic property.*

COMMENT 79: Referring to the last paragraph in Section 3.1.6, the Reviewer commented "Again, this is pure speculation, in my expert opinion. The purpose of this whole paragraph is unclear and it should be deleted altogether. No direct organ to organ concordance in tumors between humans and animals is required by any cancer hazard/risk evaluation guideline I am aware of. Quite the opposite, it is well-established that there is good concordance between animal and human carcinogens. Please see Krewski et al J Toxicol Environ Health B Crit Rev. 2019;22(7-8):203-236. doi: 10.1080/10937404.2019.1642586."

RESPONSE: *The referenced paragraph was deleted from Section 3.1.6.*

COMMENT 80: Referring to Section 3.2, the Reviewer commented "IARC 2019 lists 2 studies that identified genetic susceptibility. See section 4.4"

RESPONSE: *The Koutros et al. (2013b) and Høyer et al. (2002) studies discussed in IARC (2019) were added to Section 3.2:*

> Two studies evaluated with polymorphisms and cancer risk. In a study of single nucleotide polymorphisms, Koutros et al. (2013b) found an increased risk of prostate cancer risk among men with aldrin use and two A alleles at rs7679673 in TET2 region. The second study examined mutations in the p53 suppressor gene and breast cancer risk associated with dieldrin exposure (Høyer et al. 2002). Although no significant alterations in breast cancer risk was associated with this polymorphism, women with 'wild-type' p53 had an increased risk of dying.

COMMENT 81: Referring to Figure 6-1, the Reviewer commented "Please check on my suggestions in Section 2 of potential updates to the cancer study numbers."

RESPONSE: *See Response to Comment 51.*

COMMENT 82: Referring to Figure 6-1, the Reviewer commented "Please check on my suggestions in Section 2 of potential updates to the cancer study numbers."

RESPONSE: *See Response to Comment 52.*

COMMENT 83: Referring to Table 6-1, the Reviewer commented "Funding period should be added for clarity.

RESPONSE: *ATSDR will consider adding the funding period in future revisions of the toxicological profile guidance document.*

COMMENT 84: Referring to Table 7-1, the Reviewer commented "IARC 2019 also included references to ECHA 2016."

RESPONSE: *The focus of the regulations and guidelines listed in Table 7-1 are U.S. federal values. Although some non-country specific international guidelines (e.g., IARC, WHO) are also included, inclusion of non-U.S. country-specific values is beyond the scope of this chapter.*

COMMENT 85: Referring to the Walker et al. (1972) citation in Chapter 8, the Reviewer commented "This is actuall a 1973 reference, not 1972: Food Cosmet Toxicol 11973 June; 11(3):415-32"

RESPONSE: *The year was corrected in the reference chapter and throughout the profile.*

COMMENT 86: Referring to the statement in the aldrin acute oral MRL worksheet—The MRL is based on a LOAEL of 2 mg/kg/day for neurobehavioral effects (increased electroconvulsive shock threshold) in offspring of maternal mice administered aldrin by gavage during the third trimester of pregnancy (Al-Hachim 1971)—the Reviewer commented "In Table 2-1 this is identified as developmental endpoint. Perhaps more clarity is needed that this is "neuro-developmental"?"

RESPONSE: *The text was revised to indicate that it was a neurodevelopmental effect:*

> The MRL is based on a LOAEL of 2 mg/kg/day for neurodevelopmental effects (increased electroconvulsive shock threshold) in offspring of maternal mice administered aldrin by gavage during the third trimester of pregnancy (Al-Hachim 1971).

COMMENT 87: Referring to the statement in the aldrin intermediate oral MRL worksheet—It is not appropriate to derive an intermediate-duration oral MRL for aldrin because the lowest level tested (0.26 mg/kg/day in the 3-generation study) represents a serious LOAEL in the absence of an identified NOAEL—the Reviewer commented "I am not following this argument. Why notb use the LOAEL for "3.2-fold increased mortality of F1a pups" phenotype in Treon et al 1954a as the POD and apply a 1,000 UF to it? This is a study that is rated "high confidence" in the appendix… You acknowledge the effect is serious but would leave this effect without an MRL?"

RESPONSE: *It is ATSDR practice to not derive an MRL based on a serious LOAEL. The text was revised to clarify the issue:*

> An intermediate-duration oral MRL for aldrin was not derived because the lowest level tested (0.26 mg/kg/day in the 3-generation study) represents a serious LOAEL, and it is ATSDR practice to not base MRLs on serious LOAELs.

COMMENT 88: Referring to the rationale for not deriving an MRL in the dieldrin acute oral MRL worksheet, the Reviewer commented "This section doesn't provide a rationale for NOT deriving and acure oral MRL. It just goes over the weknessess of the database. The "Impaired escape behavior" was identified as a serious LOAEL. So why not use 0.5 mg/kg as a POD? And derive an acure oral MRL? This is a study that is rated "high confidence" in the appendix…"

RESPONSE: *As noted in the Response to Comment 87, ATSDR does not consider a serious LOAEL a suitable basis for an MRL. The text was revised to clarify this issue:*

> Thus, the lowest LOAEL was 0.5 mg/kg/day for neurological effects identified in the Carlson and Rosellini (1987) study; the study did not identify a NOAEL. The database was not considered suitable for derivation of an acute-duration oral MRL because the lowest LOAEL was considered a serious LOAEL, and it is ATSDR practice to not use a serious LOAEL as a point of departure for an MRL.

COMMENT 89: Referring to Table B-1, the Reviewer commented "Why are mechanisms not included? There is a section on putative cancer mechanisms in this document, yet I would have a hard time finding something in this table that would result in inclusion of those studies"

RESPONSE*: Although there is no specific inclusion criteria for mechanistic data, mechanistic studies are identified and evaluated along with the health outcome studies.*

COMMENT 90: Referring to Table B-2, the Reviewer commented "These strings need to be separated into sections: chemical/metabolites, health effects, species, mechanisms,. Etc. Otherwise I am not sure what the search was supposed to achieve."

RESPONSE: *ATSDR does not conduct separate literature searches for different data sets; rather one search strategy is used to identify all relevant data. Thus, it is not possible to separate the search strings.*

COMMENT 91: *Referring to the query string in Table B-2, the Reviewer commented "*This appears to be part of the search string relevant to TK and mechanistic studies. I am having a hard time understanding why these terms were included but many others, especially relevant to mechanistic evidence, were not. I suggest ATSDR use the Key characteristics serach strings that are used by IARC."

RESPONSE: *ATSDR has used these query strings (modified to be profile-specific) on most of its toxicological profiles. It has been proven to accurately identify most, if not all, studies that are relevant to the toxicological profile.*

COMMENT 92: Referring to Table C-1, the Reviewer commented "See my notes on Table B-1"

RESPONSE: *See the Response to Comment 89.*

COMMENT 93: Referring to Table C-27, the Reviewer commented "Why is it that not every study has entries in this table?"

RESPONSE: *As noted in Section C.9, the systematic review for dieldrin was conducted on studies that examined the most sensitive endpoints: hepatic, neurological, reproductive, and developmental. Studies that examined these health outcomes were included in the systematic review and in Table C-27.*

Comments provided by Peer Reviewer #3:

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1

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

COMMENT 1: I agree overall with the effects described in the draft document.

RESPONSE: *No response needed.*

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

COMMENT 2: Effects seen in animals are relevant for humans. There has been extensive discussion in the toxicology literature concerning the overall relevance of mouse liver tumors (e.g., Holsapple HP, et al. Mode of Action in Relevance of Rodent Liver Tumors to Human Cancer Risk, Toxicol Sci 89: 51–56 (2006) which has not been adequately discussed in the draft document. The ATSDR is encouraged to discuss more holistically the mechanistic data concerning a nonbenotoxic mode of action for these pesticides. This discussion is needed to provide balance – it is not intended to change the conclusions drawn by the ATSDR.

RESPONSE: *The cancer mechanistic data are discussed in Section 2.19 under the Mechanisms of Action subheading. The discussion includes genotoxic and nongenotoxic mechanisms of action specific for aldrin and dieldrin.*

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

COMMENT 3: Aldrin and dieldrin are legacy chemicals that have been banned for use and sale in the U.S. for quite some time. The reader of the summary (and main document) needs to be made aware that exposures are less likely to occur in the general population (e.g., this is raised later in the document regarding data needs). Moreover, contemporary (last 10 years) exposure data is largely lacking – inferences drawn regarding exposures from data collected in the 1970s to 1980s may overstate the risk posed to people living in the U.S..

RESPONSE: *A statement was added to Section 1.1 that general population exposure is expected to be low:*

> However, exposure to aldrin and dieldrin is expected to be low since the compounds are no longer manufactured or used in the United States. In the most recently available biomonitoring data (samples taken in 2003–2004), aldrin and dieldrin serum levels were undetectable or very low.

Minimal Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation? Please explain.

COMMENT 4: It is uclear whether sufficient data to derive acute inhalation MRLs for these compounds based on minimal effects – e.g., respiratory irritation. One justification cited appears to be the lack of inhalation exposures that occur – however, this is not a data driven exercise. The document does identify several inhalation studies that might be considered. A second stated reason that the ATSDR did not derive inhalation values is concern that the thermal sublimation process used may have led to the production of thermal degradation products. The ATSDR should critically evaluate whether this is indeed the case – e.g., Sittig's Handbook of Toxic and Hazardous Chemicals and Carcinogens (see page 95) indicates that "Aldrin is very stable thermally with no decomposition noted at 250C"). The thermal sublimation process used a temperature of 200C. The statement mentioned in Sittings is consistent with the considerably higher temperatures needed to degrade aldrin and other highly chlorinated pesticides.

RESPONSE: *In addition to the study limitations, the acute-duration inhalation database for aldrin was not considered adequate due to the limited endpoints examined in the Treon et al. (1957) study. The rationale in Appendix A was revised:*

> The Treon et al. (1957) study was not considered an adequate basis for an MRL for aldrin because the study examined a limited number of endpoints and lacked exposure concentration-response data. Given the limitations of the only available acute inhalation study, the database was not considered adequate for derivation of an acute-duration inhalation MRL for aldrin.

COMMENT 5: It is also unclear why an intermediate MLR for aldrin could not be derived from the available studies. It appears that the issue is one in which the expected gradation of MRLs (i.e., from acute to intermediate to chronic) was lacking rather than a lack of a suitable intermediate duration study (e.g., NCI 1978). Later in the document the author's state: "It is not appropriate to derive an intermediate-duration oral MRL for aldrin because the lowest level tested (0.26 mg/kg/day in the 3-generation study) represents a serious LOAEL in the absence of an identified NOAEL." – however this is inconsistent with the derivation of the acute MRL for aldrin that used an uncertainty factor of 10 to account for the lack of a NOAEL. In addition, the statement "However, because aldrin is readily converted to dieldrin in biological systems, the dieldrin intermediate-duration oral MRL for impaired task learning in monkeys should be protective for intermediate-duration oral exposure to aldrin as well." – suggests that there is a 1:1 relationship between the two – this may not be appropriate.

RESPONSE: *An intermediate-duration oral MRL was not derived for aldrin because the lowest LOAEL is for a serious health effect and it is ATSDR practice to not derive an MRL based on a serious LOAEL. The rationale for not deriving an MRL was revised in Appendix A:*

> An intermediate-duration oral MRL for aldrin was not derived because the lowest level tested (0.26 mg/kg/day in the 3-generation study) represents a serious LOAEL, and it is ATSDR practice to not base MRLs on serious LOAELs.

The statement—However because aldrin is readily converted to dieldrin in biological systems, the dieldrin intermediate-duration oral MRL for impaired task learning in monkeys should be protective for intermediate-duration oral exposure to aldrin as well—*was deleted from Section 6.2.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 6: I am concerned about the following two critical studies used to derive an MRL:

A. The acute MRL for aldrin is "based on a LOAEL of 2 mg/kg/day for neurobehavioral effects (increased electroconvulsive shock threshold) in offspring of maternal mice administered aldrin by gavage during the third trimester of pregnancy (Al-Hachim 1971)." The acute MRL is based on neurologic effects – however this study failed to show a treatment related effect of the offspring on condition avoidance response. The seizure threshold induced by an electric shock was increased in aldrin treated animals (controls 80 volts; lowdose group 109 volts). The authors did not report a dose-response for this effect. One would expect based on the postulated mechanisms (e.g., inhibition of GABA) that the seizure threshold would decrease rather than increase this threshold. GABA agonists like benzodiazepines increase the threshold (see: Chi SH, et al. Effects of Psychotropic Drugs on Seizure Threshold during Electroconvulsive Therapy. Psychiatry Investig. 2017;14(5):647-655). The finding reported by Al-Hachim has not been replicated and is very questionable to base the acute MRL on.

B. The chronic MRL for aldrin is "The MRL is based on a LOAEL of 0.037 mg/kg/day for increased liver weight and hepatic histological alterations (enlarged centrilobular hepatocytes with cytoplasmic oxyphilia, and peripheral migration of basophilic granules) in rats receiving aldrin from the food for 2 years (Fitzhugh et al. 1964). The study did not identify a NOAEL." The draft ATSDR document is misleading in some ways because no biologically significant liver lesions were seen at thus exposure dose (e.g., Fitzhugh et al report trace changes in 4/19 rats in the low dose grouo versus 1/17 in the controls ($p = 0.19$; Pearson Chi Square). ATSDR needs to independently assess this data statistically and reassess whether changes in liver weight alone would justify this study as the critical study given that this study appears to be an outlier.

RESPONSE: *Regarding the acute-duration oral MRL for aldrin, ATSDR notes that the 2 mg/kg/day point of departure for the MRL is supported by three studies conducted by Jamaluddin and Poddar (2001a, 2001b, 2003) that found increases in locomotor activity in rats. There are limited mechanistic data to accurately evaluate whether there should be an increase or decrease in seizure threshold and whether the lack of a response on the condition avoidance test is a study limitation. The Reviewer commented that the finding in the Al-Hachim (1971) study has not been replicated; ATSDR notes that no studies have attempted to replicate the findings.*

Regarding the chronic-duration oral MRL for aldrin, ATSDR considers significant increases in organ weight of target tissues to be an adverse effect. Fitzhugh et al. (1964) reported histological alterations in the liver (centrilobular hepatocellular hypertrophy) at all aldrin doses. The incidence of liver lesions was statistically significant at 0.15 mg/kg/day and higher (at 0.15 mg/kg/day, the incidence was 9/19 compared to 1/17 in controls) and there was an apparent dose-related increase in the severity of the lesions.

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

COMMENT 7: Selection of a single critical study does not follow best practices defined by the US National Academies – like RfC's developed by the US EPA it would be appropriate to develop multiple candidate MRLs.

RESPONSE: *It is not ATSDR practice to derive multiple candidate MRLs. Depending on the database, ATSDR will evaluate multiple candidate points of departure and derive a single MRL from the selected point of departure (typically the lowest point of departure).*

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature? If not, please suggest appropriate changes.

COMMENT 8: They are adequately described. One concern relates to how dog studies are classified. A 16-month study in dogs (e.g., Fitzhugh et al. 1964) is approximately 12% of a dog's lifespan (assuming a lifespan of 12 years) which is similar to a 90-day rodent study (approximately 13% of a rodent's 2-year lifespan). The dog studies should not be considered chronic – they are intermediate duration for that species.

RESPONSE: *ATSDR's definition of acute-duration, intermediate-duration, and chronic-duration is not species specific.*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT 9: They are adequately described.

RESPONSE: *No response needed.*

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT 10: Here and elsewhere, the study by Harr et al (1976) is called out with questionable relevance for using a semisynthetic diet. In some ways this may be more appropriate since open diets developed at this time may have had trace levels of these pesticides. The ATSDR needs to better justify their concerns regarding the use of this diet in the study. Another concern with this study and several others is the lack of statistical analyses by the study authors. ATSDR needs to determine whether the original data tables in this or other publications would allow them to independently assess the data using appropriate statistical methods.

RESPONSE: *The statements regarding the use of a semisynthetic diet was deleted from the profile. ATSDR was not able to conduct an independent statistical analysis of the incidence data from the Harr et al. (1970) study because the paper did not report incidence data.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT 11: Appropriate species were used.

RESPONSE: *No response needed.*

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

COMMENT 12: Adequate attention was made.

RESPONSE: *No response needed.*

QUESTION: Are you aware of any studies that are not included in the profile that 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.

COMMENT 13: I am not aware of other experimental studies. Numerous case reports have also been published in the veterinary literature.

RESPONSE: *ATSDR considers case reports in animals to be of limited value and were not added to the profile.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

COMMENT 14: I am not aware of other experimental studies that would be amenable for deriving a MRL.

RESPONSE: *No response needed.*

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

COMMENT 15: The values in the Figures do not match for some of the health outcomes – e.g., FIG 1.1. for acute neurologic effects states neurologic and developmental effects were seen at 1.5 mg/kg/day. FIG 1-3 indicates the LOAEL was 2 mg/kg/day for these endpoints. Similar concern for FIG 1-2 and FIG 1-4. A figure legend is needed that defines what the ranges of values represent (e.g., are these LOAELs?).

RESPONSE: *The y-axis in Figures 1-1 and 1-2 is presented as a range of values. The Reviewer states that Figure 1-1 indicates that neurological and developmental effects are observed at 1.5 mg/kg/day and Figure 1-3 indicates that the LOAEL is 2 mg/kg/day. Figure 1-1 indicates that the LOAEL for neurological and developmental effects are in the range of 1.5–2 mg/kg/day, which is consistent with Figure 1-3 identifying a LOAEL of 2 mg/kg/day.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT 16: These subcategories appear appropriate.

RESPONSE: *No response needed.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT 17: Discussion appears complete.

RESPONSE: *No response needed.*

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.

COMMENT 18: Overall the conclusions are supported by the data.

RESPONSE: *No response needed.*

COMMENT 19: A few considerations in Section 2.5 Cardiovascular. Changes in cholesterol are not a direct endpoint for cardiotoxicity – in many ways this reflects liver function instead. The interpretation for Black 1974 ("In the case of the man who ingested 120 mg/kg of dieldrin, the cardiovascular effects were controlled with β adrenergic blocking drugs, suggesting that the effects were due to increased sympathetic output") needs some caution since this implies a direct sympathetic effect. Dog study by Walker et al. (1969) needs to describe what cardiovascular endpoints were assessed.

RESPONSE: *The text was revised to note that the speculation that the effects were due to sympathetic overstimulation has not been confirmed:*

> The investigator suggested that the cardiovascular effects were due to sympathetic overstimulation; this hypothesis has not been confirmed with supporting data.

The text was revised to indicate that the Walker et al. (1969) study evaluated heart histopathology:

> Chronic oral exposure to doses ranging from 0.05 to 4.6 mg/kg/day did not result in histological alterations in the heart of rats, mice, or dogs (NCI 1978a; Treon et al. 1951a; Walker et al. 1969).

COMMENT 20: Section 2.9 Hepatic. The child described in Garrettson and Curley (1969) had waxing and waning changes in liver enzyme tests so this study needs to be assessed more critically. Changes in barbiturate half times could also occur due to other causes. I don't fully agree with the following interpretative statement: "The origin of the increased serum AP activity was unknown, but was not believed to be due to bone disorders or biliary obstruction (i.e., the usual clinical interpretation of elevated serum AP in dogs [Cornelius 1980; Walker et al. 1969])." Other causes including hepatic hyperplasis and other hepatobiliary disease states as well as drug exposure could account for changes in alkaline phosphatase (see: Hall RL, Everds NE. Factors affecting the interpretation of canine and nonhuman primate clinical pathology. Toxicol Pathol. 2003;31 Suppl:6-10.). As mentioned elsewhere I do not

agree with the following statement: "Hepatic lesions at an aldrin dose of 0.037 mg/kg/day were characterized by hypertrophy of centrilobular hepatocytes, cytoplasmic eosinophilia, and peripheral migration of basophilic granules along with less prominent alterations of cytoplasmic vacuolation and bile duct proliferation; these changes are consistent with an adaptive response associated with induction of the hepatic mixed function oxidase system and proliferation of smooth endoplasmic reticulum." These lesions were seen in the study but not at this dose.

RESPONSE: *Regarding the discussion of the Garrettson and Curley (1969) case report, the discussion of phenobarbital half-life as an indicator of liver function was deleted.*

A child who drank an unknown quantity of a 5% dieldrin solution and experienced severe convulsions had evidence of liver dysfunction (Garrettson and Curley 1969). Six months post-exposure, serum AP and thymol turbidity test results were elevated.

Regarding the statement—The origin of the increased serum AP activity was unknown, but was not believed to be due to bone disorders or biliary obstruction (i.e., the usual clinical interpretation of elevated serum AP in dogs [Cornelius 1980; Walker et al. 1969])—*the referenced statement was deleted.*

Regarding the results of the Fitzhugh et al. (1964) aldrin study, the text was revised:

Rats receiving aldrin from the diet for up to 2 years exhibited increased relative liver weight and hepatic histopathological changes consistent with exposure to chlorinated hydrocarbons (Fitzhugh et al. 1964). The liver effects were characterized as hypertrophy of centrilobular hepatocytes, cytoplasmic eosinophilia, and peripheral migration of basophilic granules along with less prominent alterations of cytoplasmic vacuolation and bile duct proliferation; these changes are consistent with an adaptive response associated with induction of the hepatic mixed function oxidase system and proliferation of smooth endoplasmic reticulum. Significant increases in relative liver weight was observed at ≥0.037 mg/kg/day in males and ≥0.15 mg/kg/day in females. The incidences of specific liver lesions were not included in the paper; significant increases in the total number of liver lesions were observed at ≥0.15 mg/kg/day. At 3.65 mg/kg/day, gross enlargement of the liver was observed; the histopathological changes were marked and included increased severity of hepatic cell vacuolation.

COMMENT 21: Section 2.10 Renal. " The study by Fitzhugh et al. (1964) employed only one or two rats/sex/dose" – this is incorrect the methods section states they used groups of 24 waenling rats divided by sex (i.e., n = 12 rats/sex/dose) – this is consistent with the statement they performed microscopic evaluations on 227/336 rats (page 553) and the Table reproduced in the ATSDR Appendix.

RESPONSE: *The species in the referenced text was corrected:*

The study by Fitzhugh et al. (1964) employed only one or two dogs/sex/dose

COMMENT 22: Section 2.17 Developmental. I am concerned that Harr et al (1970) is being dismissed 'too easily' – structural malformations in the brain would be quite concerning.

RESPONSE: *The interpretation of the results of the Harr et al. (1970) is limited by the lack of incidence data and/or statistical analysis, thus precluding identification of a LOAEL.*

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

Toxicokinetics

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

COMMENT 23: Minor concern Section 3.1.2 Distribution. What is meant by "The existence of a functional relationship between the concentration of dieldrin in the adipose tissue and that in the blood" – what is meant by "functional relationship"? It's unlikely that the relationship depends on any functional e.g., transporter versus driven by fat/blood solubility.

RESPONSE: *In the referenced sentence in Section 3.1.2, the term "functional" was deleted.*
The existence of a relationship between the concentration of dieldrin in the adipose tissue and that in the blood gives strong support to the concept of a dynamic equilibrium in the distribution of dieldrin between these tissues.

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

COMMENT 24: There is a pharmacokinetic model described by Garrettson and Curley (1969) that incorporates physiologic parameters and protein binding. The model was used to avaluate the time course of dieldrin in fat, musclem, and brain.

RESPONSE: *Although Garrettson and Curley (1969) used a mathematical model to compare predicted tissue levels to actual tissue levels in this one child, ATSDR did not consider this a PBPK model.*

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

COMMENT 25: This section was adequate.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

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

COMMENT 26: Relevant data has been discussed.

RESPONSE: *No response needed.*

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

COMMENT 27: Given routes of elimination its possible individuals with hepatobiliary dysfunction might have different pharmacokinetics. However, existing data does not support this hypothesis.

RESPONSE: *Given the lack of data supporting the identification of individuals with hepatobiliary dysfunction as a potentially susceptible population, this was not added to Section 3.2.*

Biomarkers of Exposure and Effect

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

COMMENT 28: No specific biomarkers of exposure are available other than determination of aldrin, dieldrin, and metabolite concentrations in biological sample.

RESPONSE: *No response needed.*

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

COMMENT 29: No specific biomarkers of effect are available.

RESPONSE: *No response needed.*

Chapter 4. Chemical and Physical Information

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

COMMENT 30: I am not aware of any errors.

RESPONSE: *No response needed.*

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

COMMENT 31: Information is provided on different forms of the chemicals.

RESPONSE: *No response needed.*

Chapter 5. Potential for Human Exposure

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

COMMENT 32: Information appears to be complete. There is a possible error in Table 5.1 suggesting that production of these chemicals is occurring in Arkansas – but elsewhere the text indicates no domestic production is occurring in the US since 1974. Table 5.2 columns do not add up (e.g., land releases sum = 7471; which is the on/off release).

RESPONSE: *Table 5-1 accurately reflects the TRI data. The total releases in Table 5-2 were corrected. The total number of on-site releases was changed to 7,454, off-site releases to 18, and on-and off site releases to 7,472.*

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

COMMENT 33: All of the above are adequately discussed.

RESPONSE: *No response needed.*

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

COMMENT 34: All of the above are adequately discussed.

RESPONSE: *No response needed.*

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

COMMENT 35: All of the above are adequately discussed.

RESPONSE: *No response needed.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT 36: All of the above are adequately discussed. One concern discussed earlier is that the text should distinguish between historical levels versis contemporary exposures. Much of the exposure data cited is one or more decades old.

RESPONSE: *As noted in the Response to Comment 3, text was added to Section 1.1 indicating the general population exposure is expected to be low. In the Overview of Chapter 5, the first bulleted statement also states that exposure is expected to be low. In Section 5.6, the text was re-arranged to discuss the most recent biomonitoring data first. The monitoring dates were included for historical data. Section 5.6 now begins with the following paragraph:*

In the Fourth National Report on Human Exposures to Environmental Chemicals (CDC 2019), aldrin levels in blood were below the level of detection for all age groups for survey years 2001–2002 and 2003–2004. Dieldrin levels in serum (lipid adjusted) are presented in Table 5-7. Geometric mean levels were not calculated because the proportion of results below the limit of detection were too high to provide a valid result.

Chapter 6. Adequacy of the Database

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

COMMENT 37: I am not aware of any studies that can fill a data gap.

RESPONSE: *No response needed.*

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

COMMENT 38: I agree – there is limited needs for new data.

RESPONSE: *No response needed.*

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

COMMENT 39: No bias was observed.

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

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

COMMENT 40: Not aware of any additional regulations or guidelines.

RESPONSE: *No response needed.*

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

COMMENT 41: All are relevant and should be included.

RESPONSE: *No response needed.*