

**Disposition of Peer Review Comments for
Toxicological Profile for Parathion**

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Prepared for:

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Comments provided by Reviewer #1

COMMENT: Charge question: *Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be?* The Reviewer responded: “The data relevant to child health and developmental effects have been adequate as they relate to available data.”

RESPONSE: *No revisions were suggested.*

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

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Does Chapter 1 present the important information in a non-technical style suitable for the average citizen? If not, suggest alternate wording.* The Reviewer responded: Chapter 1 presents important information in layman’s terms. The general public will be able to comprehend the document.

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *In your opinion, do the answers to the questions adequately address the concerns of the lay public? Are these summary statements consistent, and are they supported by the technical discussion in the remainder of the text? Please note sections that are weak and suggest ways to improve them.* The Reviewer responded: “Suggest to the question “What is parathion?” that you include in that answer that you have for “How is parathion used?”. What is listed in the first few words of that statement is more suitable for “What is parathion?”. For example, “Parathion is the common name of a formerly used organophosphorus insecticide used to control sucking and chewing insects and mites in a wide variety of crops.” To answer the question regarding how parathion is used, perhaps you should mentioned various ways in which the chemical is applied.”

RESPONSE: *The revisions were made as suggested.*

COMMENT: Charge question: *Are scientific terms used that are too technical or that require additional explanation? Please note such terms and suggest alternate wording.* The Reviewer responded: “No, terms have been adequately explained where needed. Chapter 1 isn’t too technical for the general public.”

RESPONSE: *No revisions were suggested.*

COMMENT: The Reviewer identified a reference discrepancy on page 9, stating that the references activities that took place in 2002 and 2003; however, the reference from which this referenced information was acquired is 2000 (2–3 years after the published reference).

RESPONSE: *The revision was made as to show consistency with the citation.*

COMMENT: The Reviewer identified a typographical error on page 20, the word *no* needs to be changed with the word *not*.

RESPONSE: *The revision was made as suggested.*

COMMENT: Charge question: *Do you agree with those effects known to occur in humans as reported in the text? If not, provide a copy of additional references you would cite and indicate where (in the text) these references should be included.* The Reviewer responded: “The effects listed in the text as they related to human occurrence adequately address the data available and thus, I agree with the listed health effects.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge 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.* The Reviewer responded: “Those effects observed in animals were, in most cases, observed in human volunteer or intentional exposure studies.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Have exposure conditions been adequately described? If you do not agree, please explain.* The Reviewer responded: “Exposure conditions have been adequately described. The document gives a comprehensive review of parathion exposure routes.”

RESPONSE: *No revisions were suggested.*

COMMENT: To the question of whether a brief substance-specific discussion may be added to Section 3.1, **INTRODUCTION**, to explain a complex topic, the Reviewer responded: “No additional information to add to this section.”

RESPONSE: *No revisions were suggested.*

Section 3.2, DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

Were the appropriate statistical tests used in the studies? Would other statistical tests have been more appropriate? Were statistical test results of study data evaluated properly? NOTE: As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data. Are you aware of other studies which may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

The Reviewer stated: “The text provided a very detailed human studies discussion. Where data were limited, writers noted the limitations generally, except in the cases of the effect of inhaled parathion on reproduction, development and cancer. I suggest indicating that data isn’t available at the present time for those sections. The sections presented studies that contain appropriate statistical tests, and appropriate NOAELs and/or LOAELs were noted where available. Where not available, the writers indicated the rationale behind not providing NOAELs and/or LOAELs. After reviewing the data provided and searching available publications, I have no additional suggestions regarding the inclusion of other studies.”

RESPONSE: *There is a sentence before the headings for reproduction, development, and cancer stating that no information was located for those end points.*

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

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

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

Were the appropriate statistical tests used in the studies? Would other statistical tests have been more appropriate? Were statistical test results of study data evaluated properly? NOTE: As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data. Are you aware of other studies which may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

The Reviewer responded: “As with the review of human studies, the text provided a very detailed human studies discussion. Where data were limited, writers noted the limitations generally, except in the cases of the effect of inhaled parathion on reproduction, development and cancer. I suggest indicating that data isn’t available at the present time for those sections. The sections presented studies that contain appropriate statistical tests, and appropriate NOAELs and/or LOAELs were noted where available. Where not available, the writers indicated the rationale behind not providing NOAELs and/or LOAELs. After reviewing the data provided and searching available publications, I have no additional suggestions regarding the inclusion of other studies.”

RESPONSE: *There is a sentence before the headings for reproduction, development, and cancer stating that no information was located for those end points.*

COMMENT: The following charge questions were posed to the Reviewer regarding the LSE Tables and Figures:

Are the LSE tables and figures complete and self-explanatory? Does the "Users Guide" explain clearly how to use them? Are exposure levels (units, dose) accurately presented for the route of exposure?

Please offer suggestions to improve the effectiveness of the LSE tables and figures and the "User's Guide." Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?

If MRLs have been derived, are the values justifiable? If no MRLs have been derived, do you agree that the data do not support such a derivation?

The Reviewer responded: "The Levels of Significant Exposure and Tables as well as the accompanying "User Guide" provided an adequate overview of available data. The "User Guide" gives a detailed overview of how to use the LSE tables. LSE tables were descriptive and complete given available data. All listed MRL's were justifiable. Areas with lacking MRL's were justified as well."

RESPONSE: *No revisions were suggested.*

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

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

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.

Has adequate attention been paid to dose-response relationships for both human and animal data?

Please explain.

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

The Reviewer responded: "Overall, the toxicological profile for parathion is well written and provides detailed descriptions of available data. Conclusions associated with provided data were adequately drawn and provided in a manner that allows the reader to understand not only the areas where studies were more detailed, but areas where data were lacking as well. Dose-response relationships, where available, were detailed using appropriate animal models. Additionally, where sufficient animal data were available, proper conclusions were used to draw support for known human effects. It appears that careful consideration was given to all drawn conclusions."

RESPONSE: *No revisions were suggested.*

Section 3.4, TOXICOKINETICS

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

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

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

*Is there adequate discussion of the differences in toxicokinetics between humans and animals? What other observations should be made? Is there an **adequate** discussion of the relevance of animal toxicokinetic information for humans? If not, please explain.*

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

The Reviewer responded: "Given the available data, this section adequately discusses absorption, distribution, metabolism and excretion of parathion. I would suggest, however, that some sections (e.g., absorption: inhalation exposure) be revisited once more sufficient animal data is available as it is extremely lacking in that area. This section provides an adequate overview of all metabolic parameters and pharmacokinetic/pharmacodynamics models available. This discussion regarding is very detailed.

Yes, all major storage organs have been identified. Data also suggests organs that are more susceptible. Considering available data, suggested information is adequate; however, I suggest revisiting this section once additional oral and dermal animal studies as well as inhalation absorption data are available. This could possibly allow of extrapolation of data for human health suggestions. There was no discussion regarding different forms of parathion. The Reviewer, however, asked ATSDR to consider adding a study by Kamataki et al. (1976) regarding the metabolism of parathion in rabbit liver microsomes. The complete reference was not provided.”

RESPONSE: *ATSDR obtained and reviewed the reference suggested by the Reviewer and added pertinent text to Section 3.4.3, Metabolism.*

COMMENT: The Reviewer identified a typographical error, removing the space from “lead ing”.

RESPONSE: *The typographical error was corrected.*

Section 3.5, MECHANISMS OF ACTION

COMMENT: Charge question: *Have all possible mechanisms of action been discussed? If not, please explain.* The Reviewer asked ATSDR to consider adding a paper by Bajgar (2004), a review publication. The complete reference was not provided.

RESPONSE: *The reference suggested by the Reviewer was added in Section 3.5.2, Mechanisms of Toxicity.*

Section 3.8, BIOMARKERS OF EXPOSURE AND EFFECT

COMMENT: Charge questions: *Are the biomarkers of exposure specific for the substance or are they for a class of substances? If they are not specific, how would you change the text? Are there valid tests to measure the biomarker of exposure? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.*

The Reviewer responded: “There are biomarkers of exposure for parathion and its metabolites in tissues and body fluids for both lower levels of exposure as well as higher levels of exposure. This section does not mention specific tests used to measure biomarker exposures for parathion rather it mentions the outcome that is measure. It mentions the measurement of metabolites in certain body fluids and tissues as well as measuring AChE inhibition. There are no inconsistencies.”

RESPONSE: *No revisions were suggested.*

Section 3.9, INTERACTIONS WITH OTHER CHEMICALS

COMMENT: Charge question: *Is there adequate discussion of the interactive effects with other substances?* The Reviewer responded by suggesting adding data from a paper by Qiao et al. (1996).

RESPONSE: *Data from Qiao et al. (1996) were added to subsection 3.4.1.3, Dermal Exposure in Section 3.4, TOXICOKINETICS, since the study examined how various chemicals influenced parathion absorption in the isolated perfused porcine skin.*

COMMENT: Charge question: *Does the discussion concentrate on those effects that might occur at hazardous waste sites? If not, please clarify and add additional references.* The Reviewer responded:

“The discussion does not concentration on effects that might occur at hazardous waste sites. Further research yielded no studies on the interactive effects of parathion and other chemicals in hazardous waste site.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? If not, please clarify and provide any appropriate references.* The Reviewer responded: “Yes, the text discusses whether the interactive effects contributed to the activation or detoxification pathways of parathion or whether parathion affected certain enzymes as a result of combined exposure.”

RESPONSE: *No revisions were suggested.*

Section 3.10, POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

COMMENT: Charge question: *Is there a discussion of populations at higher risk because of biological differences which make them more susceptible?* The Reviewer responded: “This adequately discusses populations at higher risk and the circumstances surrounding their increased susceptibility.”

RESPONSE: *No revisions were suggested.*

COMMENT Charge questions: *Do you agree with the choices of populations? Why or why not? Are you aware of additional studies in this area?* The Reviewer responded: “The selected populations address areas of particular concern: areas in developing countries as well as those who have a genetic predisposition.”

RESPONSE: *No revisions were suggested.*

Section 11, METHODS FOR REDUCING TOXIC EFFECTS

COMMENT: Charge questions: *Is the management and treatment specific for the substance, or is it general for a class of substances? Is there any controversy associated with the treatment? Is it a “well accepted” treatment? Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?* The Reviewer responded: “This section discusses the management and treatment of exposure specific to parathion. While there are limitations noted for certain treatment options, the options include recommendations regarding use of certain treatment options as well as alternative options; therefore, this section adequately addresses treatment options. Suggestion: Page 106, paragraph 2, line 22 may best fit if it is reworded and possible cited. The following statement is of concern: “The removal of clothing eliminated 85-90% of a contamination hazard.” Perhaps, it may best fit if stated as: The removal of clothing should eliminate 85–90% of a contamination hazard; or, include the citation left as is.”

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

COMMENT: Charge questions: *Are treatments available to prevent the specific substance from reaching the target organ(s), or are the actions general for a class of substances? Is there any controversy associated with the treatment? Is it a “well-accepted” treatment? If the discussion concerns*

an experimental method, do you agree with the conceptual approach of the method? Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)? Are there treatments to prevent adverse effects as the substance is being eliminated from the major organs/tissues where it has been stored (e.g., as a substance is eliminated from adipose tissue, can we prevent adverse effects from occurring in the target organ[s])? The Reviewer responded: “Because parathion is rapidly eliminated from the body, controlling the symptoms are of primary concern. These treatments are adequately addressed.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge questions: *Are treatments available to prevent the specific substance from reaching the target organ(s), or are the treatment's actions general for a class of substances? Is there any controversy associated with the treatment? Is it a "well accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method? Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?* The Reviewer responded: “This section adequately addresses areas of concern affected by parathion exposure and the treatments available to minimize exposure as well as decrease LD₅₀ values. Additionally, it addresses necessary treatment limitations for children as well as adults.”

RESPONSE: *No revisions were suggested.*

Section 3.12, ADEQUACY OF THE DATABASE.

COMMENT: Charge question: *Do you know of other studies that may fill a data gap? If so, please provide the reference.* The Reviewer responded: “This table (Table 3-5) adequately addresses/notes where data gaps are. After further research of publications, no additional studies are currently available.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge questions: *Are the data needs presented in a neutral, non-judgmental fashion? Please note where the text shows bias. Do you agree with the identified data needs? If not, please explain your response and support your conclusions with appropriate references. Does the text indicate whether any information on the data need exists? Does the text adequately justify why further development of the data need would be desirable; or, conversely, justify the "inappropriateness" of developing the data need at present? If not, how can this justification be improved.* The Reviewer responded: “Appropriate data needs have been identified, and they have been presented in a neutral, non-judgmental fashion. The text indicates that further data needs exist and why this need will further allow us to understand the effects of parathion exposure as well as understanding on various toxicological endpoints in various subjects. Ongoing studies were also extensive and adequately addressed. The table provides a clear understanding of possible forthcoming data.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Have exposure conditions been adequately described? If you do not agree, please explain.* The Reviewer responded: “Exposure conditions have been adequately described. The document gives a comprehensive review of parathion exposure routes.”

RESPONSE: *No revisions were suggested.*

COMMENT: To the charge questions addressing Chapter 4: *Are you aware of any information or values that are wrong or missing in the chemical and physical properties tables? Please provide appropriate references for your additions or changes. Is information provided on the various forms of the substance? If not, please explain.* The Reviewer responded: “This section adequately addresses the physiochemical characteristics of parathion. This section lists various formulations of parathion and concentrations.”

RESPONSE: *No revisions were suggested.*

COMMENT: To the charge questions addressing Chapter 5: *Are you aware of any information that is wrong or missing? If so, please provide copies of the references and indicate where (in the text) the references should be included.* The Reviewer responded: “There is no missing or incorrect information. This section adequately addresses production, import/export, use and disposal of parathion. It also addresses best practices for disposal of parathion.”

RESPONSE: *No revisions were suggested.*

COMMENT: To the following charge question addressing Chapter 6: *Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.* The Reviewer responded: “The text appropriately traces parathion from its release point to the environment until it reaches a receptor organism. Additionally, the text provides adequate and technically sound information regarding NPL sites including the number of specified locations.”

RESPONSE: *No revisions were suggested.*

COMMENT: To the following charge question addressing Chapter 6: *Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.* The Reviewer responded: “Transport, partitioning, transformation and degradation of parathion in all media areas are adequately addressed.”

RESPONSE: *No revisions were suggested.*

COMMENT: To the following charge question addressing Chapter 6: *Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.* The Reviewer responded: “This section adequately addresses parathion levels monitored or estimated in the environment.”

RESPONSE: *No revisions were suggested.*

COMMENT: To the following charge question addressing Chapter 6: *Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?* The Reviewer responded: “Although there is limited current data regarding parathion exposure in humans (due to cancellation of production and use), sufficient historical data is presented to assess the effect that parathion exposure has on the general population and occupational exposure. Specifically, historical data related to exposure of children was adequately discussed.”

RESPONSE: *No revisions were suggested.*

COMMENT: The following charge questions were posed to the reviewer regarding Sections 6.8.1, Identification of Data Needs and 6.8.2, Ongoing Studies: *Are the data needs presented in a neutral, non-judgmental fashion? Please note where the text shows bias. Do you agree with the identified data needs? If not, please explain your response and support your conclusions with appropriate references. Does the text indicate whether any information on the data need exists? Does the text adequately justify why further development of the data need would be desirable; or, conversely, justify the "inappropriateness" of developing the data need at present? If not, how can this justification be improved.* The Reviewer responded: “Appropriate data needs have been identified, and they have been presented in a neutral, non-judgmental fashion. The text indicates that further data needs exist and why this need will further allow us to understand the molecular effects of parathion as well as understanding exposure levels in environmental media.”

RESPONSE: *No revisions were suggested.*

COMMENT: To the following charge questions addressing Chapter 7: *Are you aware of additional methods that can be added to the tables? If so, please provide copies of appropriate references. Have methods been included for measuring key metabolites mentioned previously in the text? If unique issues related to sampling for the substance exist, have they been adequately addressed in the text? What other discussion should be provided?* The Reviewer responded: “This section sufficiently details methods for detecting parathion in various samples as well as outlines data using detection methods.”

RESPONSE: *No revisions were suggested.*

COMMENT: The following charge questions were posed to the reviewer regarding Section 7.3.1, Identification of Data Needs: *Are the data needs presented in a neutral, non-judgmental fashion? Please note where the text shows bias. Do you agree with the identified data needs? If not, please explain your response and support your conclusions with appropriate references. Does the text indicate whether any information on the data need exists? Does the text adequately justify why further development of the data need would be desirable; or, conversely, justify the "inappropriateness" of developing the data need at present? If not, how can this justification be improved.* The Reviewer responded: “Data needs are presented in a neutral, non-judgmental fashion and appropriate discussion regarding the need for additional data was noted. The text adequately identifies areas where additional data would be more beneficial.”

RESPONSE: *No revisions were suggested.*

Chapter 8, REGULATIONS AND ADVISORIES

COMMENT: Charge question: *Are you aware of other regulations or guidelines that may be appropriate for the table? If so, please provide a copy of the reference.* The Reviewer responded: "Appropriate recommendations and requirements have been addressed. This section covers regulatory and advisory agencies that are appropriate for a detailed discussion."

RESPONSE: *No revisions were suggested.*

Chapter 9, REFERENCES

COMMENT: Charge question: *Are you aware of other regulations or guidelines that may be appropriate for the table? If so, please provide a copy of the reference.* The Reviewer responded: "Additional references, where suggested, have been discussed in previous areas of this document. Currently listed references are complete, excluding where suggestions were made."

RESPONSE: *References were added where appropriate, as previously discussed.*

Comments provided by Reviewer #2

GENERAL COMMENT 1: The Reviewer notes that there is no information provided on the potential for human exposure related to the contaminated waste sites listed on the EPA National Priorities List (NPL). As parathion use is no longer permitted, contamination from these sites would be the most likely exposure source to the general population. The Reviewer suggests the inclusion of some discussion on the potential for exposure from these sites, such as levels of parathion measured in different media, the potential for parathion to transport offsite, and data from any site assessments, as well as a table dedicated to summarizing the environmental contamination at these 21 sites.

RESPONSE: *There is limited data that can be obtained from the HazDat data. There were 54 detections at 21 unique sites. A table summarizing this information along with the media in which they were detected was added to the profile. Maximum concentrations were reported by NPL, but because ATSDR does not have access to the key providing the units of these concentrations, they cannot be reported. The potential for exposure to the general public from contaminated waste sites could be possible by volatilization from soil to the atmosphere, to surface water via runoff, and to groundwater from leaching. However, as parathion degrades relatively rapidly in each environmental compartment, human exposure from waste sites is expected to be minimal. This information is contained in the profile in Section 6.5.*

GENERAL COMMENT 2: The Reviewer references the California Department of Pesticide Regulation (CDPR) Pesticide Use Reporting (PUR) report as having some limited use of parathion in California agriculture: 241 pounds in 2001. The PUR document is not clear as to whether these are reporting errors; however, a personal communication between the Reviewer and a CDPR representative indicated that the data may reflect actual use. The Reviewer asks that this information be clarified.

RESPONSE: *The use of parathion in the United States became illegal on October 31, 2003. It is most likely that the reported use of parathion to the PUR by pesticide users is a reporting error and that the pesticide actually used was methyl parathion. Methyl parathion was still a restricted use, registered product in the country in 2011. No revisions were made to the profile.*

GENERAL COMMENT 3: The Reviewer suggests that current information on the international use of parathion be included in the profile, along with information on the commodities treated.

RESPONSE: *International data are typically beyond the scope of ATSDR guidelines for preparing toxicological profiles. Also, a list of the international use of parathion and the commodities it is used on is not likely to be comprehensive or accurate. Commodities treated with parathion in other countries are not allowed to be imported into the United States as stated by the EPA and NAFTA guidance. This import restriction information was added to the profile.*

GENERAL COMMENT 4: The Reviewer notes that the vast majority of exposure and environmental contamination information is outdated and is not relevant to current conditions since parathion use declined so drastically. The only recent data are air monitoring data from Canada. The Reviewer suggests including some discussion of the source of parathion in these air samples and the relevance to U.S. conditions.

RESPONSE: *International data are typically beyond the scope of ATSDR guidelines for preparing toxicological profiles. A statement was added to the profile to explain that parathion may be found in environmental media in agricultural regions of countries that still use parathion. The United States is not likely to be affected by international contamination due to parathion's relatively rapid degradation in the environment.*

GENERAL COMMENT 5: The Reviewer notes that it would be helpful to add a section and/or table that summarizes all recent information on use, environmental contamination, and exposure to the extent that information exists, since December 13, 2006, when the Drexel registration was cancelled. The Reviewer also notes that while a large amount of contamination and exposure data has been reviewed, it is not relevant to today's environment. The Reviewer suggests a brief review focusing on a more recent time frame.

RESPONSE: *Data on recent use, contamination, and exposure could not be located, as production and use of this chemical was cancelled in the United States. This lack of data was noted in various sections throughout the profile. The profile also states that since parathion use was cancelled over a decade ago, exposure to the general population is expected to be low. No revisions were made to the text.*

GENERAL COMMENT 6: The Reviewer notes that in several instances, the document cites epidemiologic studies that used *p*-nitrophenol as biomarker of exposure to parathion, including data from NHANES and Eskenazi et al. (2004). However, the Reviewer further notes that *p*-nitrophenol is not specific for parathion and can be derived from other pesticides such as methyl-parathion and non-pesticidal sources such as *p*-nitrobenzene. Given these limitations, the Reviewer suggests both NHANES data and the Eskenazi et al. (2004) study should be used with extreme caution, and heavily caveated wherever cited.

RESPONSE: *NHANES is mentioned once in the document (Section 6.5) and Eskenazi et al. (2004) is mentioned numerous times (Chapters 1, 2, and 3). Statements were already in several places indicating the lack of specificity of *p*-nitrophenol as biomarker for parathion exposure and have now been added where caveats were missing.*

GENERAL COMMENT 7: The Reviewer recommends changing the classification of diarrhea in record #3 in Table 3-1 from less serious to serious.

RESPONSE: *The Reviewer's recommendation was followed.*

GENERAL COMMENT 8: The Reviewer states the following: "Numerous human dosing studies were reviewed to evaluate pharmacokinetics and toxicological information. Given recent controversy over the use of human dosing studies in pesticide registration, a section reviewing the ethics of pesticide human dosing should be included, and whether the studies reviewed and/or used for the establishment of MRL would meet modern standards, and, if not, justification on use of the information." The Reviewer further states the following regarding the human study that was used as the basis for the intermediate-duration oral study for parathion: "This study was a human dosing study. Study subjects were prisoners in San Quentin State Prison and the California Medical Facility in Vacaville, both in California. No information on the consent process is provided, a key requirement of all subject research published today."

RESPONSE: *ATSDR endorses the highest ethical standards in conducting human dosing studies. Thus, the Rider et al study raises ethical concerns about human subjects' protection and would not be approved today based on the current human subject protection regulations (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc>). The participants in the study were prisoners in San Quentin State prison and the California Medical Facility in Vacaville, raising questions about their ability to make a truly voluntary and uncoerced decision whether or not to participate in the study. The study report provides no detailed information regarding consent procedures other than to state that the participants were volunteers. ATSDR believes that the use of the study is consistent with the recommendations by the NRC (2004. *Intentional human dosing studies for EPA regulatory purposes: Scientific and ethical issues*. Washington, DC: The National Academies Press, National Research Council). Recommendation 4-1 states that: "EPA should consider a human dosing study intended to reduce the interspecies uncertainty factor (for example, a study of a biomarker such as cholinesterase inhibition) as conferring a societal benefit only if it was designed and conducted in a manner that would improve the scientific accuracy of EPA's extrapolation from animal to human data."*

Although there is limited information about the consent procedures used in this study, the information that is provided about the participants being volunteers suggests that there is no clear and convincing evidence that the conduct of this study was fundamentally unethical.

As discussed in the profile, the available intermediate-duration oral studies suggest that in humans, rats, and dogs, significant inhibition (>20%) of red blood cell AChE activity occurs with repeated doses ≥ 0.1 mg parathion/kg/day. The human study by Rider et al. (1969) provides a basis for an MRL that improves the accuracy of the value based on the animal data alone, and eliminates the interspecies uncertainty factor. Any human dosing study must have a useful purpose and convey a benefit to participants and/or society (NRC, 2004). ATSDR believes that the Rider et al. (1969) study provides a benefit to society in that the data provide the basis for a health guidance value (i.e., MRL) that can be used to protect exposed populations to parathion.

A review of the ethics of pesticide human dosing in the toxicological profile is outside the scope and intent of the profile; however, ATSDR has provided a statement in the Appendix A discussion of the oral intermediate MRL, and provided reference citations to NRC (2004).

GENERAL COMMENT 9: The Reviewer states that more information is warranted on the unique vulnerabilities of children to hazardous substances and pesticides. The Reviewer notes that ATSDR should consider reviewing and citing information found Eskenazi et al. (1999). The Reviewer further states that the studies by Slotkin and coworkers need additional highlights because they report effects of some organophosphorus pesticides that appear unrelated to inhibition of acetylcholinesterase.

RESPONSE: *The review article by Eskenazi et al. (1999) cites four studies with information relevant to parathion: Pope et al. (1991), Pope and Chakraborti (1992), Stamper et al. (1988), and Veronesi and Pope (1990). Information from the two studies by Pope and coworkers was added to Section 3.7, CHILDREN'S SUSCEPTIBILITY, whereas information from the other two references was added to Section 3.2.4, Other Routes of Exposure. ATSDR feels that the Slotkin studies have been given appropriate mention both in Section 3.2.4 and Section 3.5.2, Mechanisms of Action, particularly since the animals are treated by subcutaneous injection, a non-relevant route of exposure.*

GENERAL COMMENT 10: The Reviewer notes that the profile does not cite the Food Quality Protection Act (FQPA 1996). According to the Reviewer, the FQPA directed EPA to consider the vulnerability of sensitive subpopulations, including children. The Reviewer states that there should be an

explicit or listing as to whether an FQPA factor for children (range 1–10) should be considered, or if not, why not. The Reviewer provided a list of 10 studies that seem to deal with paraoxonase 1 (PON1), an A-esterase that hydrolyzes paraoxon, the active metabolite of parathion. The Reviewer’s point seems to be that because PON1 activity has been shown to be lower in young children, they might be more susceptible to the effects of parathion.

RESPONSE: *FQPA safety factors are not among the standard uncertainty factors used by ATSDR. However, if there were compelling evidence indicating that young children might be more vulnerable to the effects of parathion (i.e., due to lower PON1 activity), ATSDR would consider using a modifying factor to adjust an MRL appropriately. Information regarding PON1 is provided in Section 3.10, POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE, taken from the recent review by Costa et al. (2013). The section has been expanded with information about PON1 activity being developmentally regulated. The following is part of the text that has been added: “Human studies have shown that PON1 activity is very low at birth and increases over time reaching a plateau between 6 months and a few years of age. There are also data indicating that PON1 activity may be even lower before birth as determined in premature babies compared to term babies. While this suggests that fetuses and young children may be at higher risk of organophosphate toxicity, it may not be the case regarding parathion based on data from studies with rat liver microsomes and human liver microsomes that have suggested that PON1 is not functionally important at the toxicologically relevant concentrations of paraoxon (Chambers et al. 1994; Mutch et al. 1999).”*

Based on the data suggesting that PON1 is not functionally important at the toxicologically relevant concentrations, the fact that there was not significant exposure to parathion (if any) in the subjects studied in the papers listed by the Reviewer (exposure was mostly to chlorpyrifos, diazinon, malathion, and oxydemeton-methyl according to Bouchard et al. 2011), and that the profile is about parathion, ATSDR believes that it is unnecessary to include in the profile information from the papers listed by the Reviewer.

PUBLIC HEALTH STATEMENT:

COMMENT: Charge question: *Are the summary statements consistent, and are they supported by the technical discussion in the remainder of the text?* The Reviewer responded: “Generally yes. Please note my critique of Eskenazi et al. (2004).”

RESPONSE: *Please see response above to GENERAL COMMENT 6.*

COMMENT: Regarding the statement: “Once in the body, parathion distributes primarily to the liver where it is broken down into other chemicals (metabolites),” the Reviewer stated the following: “This depends in part on route. Difference between oral/dermal/inhalation should be described here.”

RESPONSE: *The following sentence was added: “Less parathion will reach the liver if it is inhaled or there is skin contact than if it is ingested.”*

COMMENT: The comment refers to the following statement: “People who ingested parathion either intentionally or in contaminated food, who were exposed during application of the pesticide to fields, or who entered areas that had been sprayed too soon after application of this substance suffered excessive eye watering and salivation, blurred vision, stomach cramps, diarrhea, difficulty breathing, tremors, and seizures, and some died.” The Reviewer states that diarrhea should be considered a serious effect (see responses to GENERAL COMMENT 7 above).

RESPONSE: *As indicated in the response to GENERAL COMMENT 7, the classification of diarrhea was changed from less serious to serious in Table 3-1.*

COMMENT: The Reviewer suggests adding the following paragraph: “More recent studies of other similar pesticides found that long-term exposure might result in neurological problems in children. Because parathion is in the same class as these other pesticides, parathion may cause similar problems.” The Reviewer suggested three citations for the statement (Bouchard et al. 2011; Eskenazi et al. 2007; Rauh et al. 2011) and provided a series of related studies to be considered for inclusion.

RESPONSE: *The following statement was added: “More recent studies of other similar pesticides found that long-term exposure might result in neurological problems in children (Bouchard et al. 2011; Eskenazi et al. 2007; Rauh et al. 2011). However, although parathion is in the same class as these other pesticides, it has not been directly implicated in the neurological alterations reported in these or other studies of children. ATSDR believes the above paragraph reflects more accurately the findings of the studies provided by the Reviewer.*

RELEVANCE TO PUBLIC HEALTH

COMMENT: Charge 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.* The Reviewer responded: “Information on animals and human studies are adequately described.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding the section **HEALTH EFFECTS**, the Reviewer stated the following: “More information on neurological effects of OPs in young children warranted. Not specific to parathion, but likely relevant. See references above.”

RESPONSE: *Please see above responses to GENERAL COMMENTS 9 and 10 and to a comment regarding the PUBLIC HEALTH STATEMENT above.*

COMMENT: The Reviewer stated the following regarding **DISCUSSION OF EFFECTS BY ROUTE OF EXPOSURE**: “Tables and studies appear adequate. Note comments above about diarrhea as serious effect. One factor seems to present a slight disconnect. Lethal doses are described in the text as: Estimates of lethal doses range from about 2 to 13 mg/kg in adults (assuming 70 kg body weight) and from 0.1 to 1.3 mg/kg in children (Gallo and Lawryk 1991). Yet many of the tox studies to doses that are higher. This raises several issues: (1) There is an order of magnitude difference in the sensitivity of children with this crude measure of toxicity. This should be discussed somewhere. (2) Many of the tox studies evaluated higher exposures, even with less serious effects. For example, doses at 16 mg/kg/day were evaluated in mice by Casale et al. (1984), including 20% lethality. This report is also cited for less serious effects (IgM suppression). I recommend that only the most serious effect from a given study/dose range be presented. The IgM information at 16 mg/kg/day is not relevant given the severity of the dose and other effects. (3) Some studies report NOAELs that just don’t make sense given the lethality. For example, a NOAEL of 4 mg/kg/once exposure for altered neurological functioning in male rats is reported for Moser (1995) in Table 3-2, a level at the lethal dose in some adults and exceeding the lethal dose in children. Perhaps this is an example of differences between of differences between humans and animals, however, these results don’t seem consistent given the severity of effects in humans. It would be helpful

if the tables included a code judging the quality of the study, and perhaps some of these anomalies can be discussed in terms of study quality, extrapolation between species, etc.”

RESPONSE: *The following paragraph was added at the end of Section 3.2.2.1, Death, as a possible explanation for the apparent disconnect between lethal doses in humans and doses used in animal studies: “However, Gallo and Lawryk (1991) also indicate that there have been reports of patients who survived after ingesting 20,000–40,000 mg parathion and that prompt treatment with oximes can save some patients who have ingested as much as 50,000 mg parathion. In addition to potentially unreliable estimates, whether or not proper treatment was implemented after poisoning and how fast this was done probably impacted the outcome and contributed to the wide range of lethal doses reported for parathion in humans.” In addition, for studies that reported lethality and additional effects (i.e., immunological effects), a statement was added to the comment field of the record for immunological effects in Table 3-2 indicating that the dose levels listed also caused lethality (see the revised entry for Casale et al. 1984 in Table 3-2). Regarding including a code judging the quality of the study, ATSDR will consider the Reviewer’s suggestion for future profiles.*

COMMENT: The following charge question was posed to the Reviewer regarding **QUALITY OF HUMAN STUDIES:** *Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)?* The Reviewer responded: “See comments above regarding human dosing studies, FQPA, and Eskenazi et al. 2004 exposure issues.”

RESPONSE: *Please see responses above for these specific comments.*

COMMENT: The following charge question was posed to the Reviewer regarding **QUALITY OF HUMAN STUDIES:** *Are you aware of other studies which may be important in evaluating the toxicity of the substance?* The Reviewer responded: “See comments above.”

RESPONSE: *Please see response to comments above.*

COMMENT: The following charge question was posed to the Reviewer regarding **QUALITY OF ANIMAL STUDIES:** *Were the animal species appropriate for the most significant toxicological endpoints of the study?* The Reviewer responded: “See comments above. Note, suggest using single most severe outcome for single dose range in a study as the key finding.”

RESPONSE: *Listing all of the end points monitored in the study (affected by treatment or not) is in accordance with ATSDR’s guidance. ATSDR agrees that if an effect occurred at a lethal dose level this should be mentioned in the text and included in the Comment field of the LSE tables.*

COMMENT: “A 1-hour LC₅₀ of 137 mg/m³ was calculated for technical parathion in female Sprague-Dawley rats (EPA 1978). The report also states that the 1-hour LC₅₀ in male rats was 1,070 mg/m³.” In reference to the above statements in the profile, the Reviewer has the following comments: “Sex differences in the tox studies were interesting. Any impact on safety factors used in MRLs? Human variability factor of 10 adequate?”

RESPONSE: *The almost 10-fold difference in LC₅₀ values between male and female rats reported in the EPA (1978) study is probably a typographical error. An LC₅₀ of 1,070 mg/m³ could not have been*

calculated if the rats were exposed to concentrations of parathion of 63, 98, 142, and 193 mg/m³. To avoid misinterpretation of the data, the reported male LD₅₀ of 1,070 mg/kg was deleted. Regrettably, no other study tested the acute inhalation toxicity of parathion in male and female animals. Oral studies suggest that females are more sensitive to the acute effects of parathion than males (see Table 3-2); this is mentioned in the profile. Differences in LD₅₀ values ranged from 1.8-fold to 3.6-fold. No such difference was seen in mice in a 2-week study (NCI 1979). In the absence of information indicating a significant difference (i.e., 10-fold or more) in susceptibility between males and females, a human variability factor of 10 seems appropriate. No revisions were made.

COMMENT: The following charge question was posed to the Reviewer regarding the **LEVELS OF SIGNIFICANT EXPOSURE (LSE) TABLES AND FIGURES**: *Are the LSE tables and figures complete and self-explanatory?* The Reviewer responded: “Overall I found these very useful. See above comments.”

RESPONSE: *See responses to above comments.*

COMMENT: The following charge question was posed to the Reviewer regarding the **LEVELS OF SIGNIFICANT EXPOSURE (LSE) TABLES AND FIGURES**: *Do you agree with the categorization of “less serious” for the effects cited in the LSE tables?* The Reviewer responded: “See comments above. Note, I would consider cholinesterase inhibition between 50 and 60% “serious” not “less serious”.”

RESPONSE: *Please see responses to above comments. According to ATSDR’s guidance, 20–59% inhibition is classified as “less serious” and 60% or greater as “serious”.*

COMMENT: The following charge question was posed to the Reviewer regarding **EVALUATION OF TEXT**: *Have the major limitations of the studies been adequately and accurately discussed? How might discussions be changed to improve or more accurately reflect the proper interpretations of the studies?* The Reviewer responded: “See comments above and embedded track changes.”

RESPONSE: *See responses to above comments.*

COMMENT: The Reviewer commented on the following text in subsection 3.4.2.4, **Other Routes of Exposure** in Section 2.4, **TOXICOKINETICS**: “The distribution of parathion from blood to liver after intraperitoneal injection of 5 mg/kg was lower in pregnant mice (liver:blood ratio of 1.42) than in virgin mice (liver:blood ratio of 15.35) (Weitman et al. 1986). The authors postulated that the higher blood concentrations of parathion in pregnant mice would be available for extrahepatic activation and result in the higher toxicity of this compound in pregnant animals”. The Reviewer’s comment was the following: “Very interesting. Possibly basis for FQPA safety factor for fetus?”

RESPONSE: *As indicated above, FQPA safety factors are not among the standard uncertainty factors used by ATSDR; however, if there were strong evidence of increased vulnerability, a modifying factor could be used. There are no studies in humans showing or suggesting that the fetus is affected by maternal exposure to parathion and the sole study by Weitman et al. (1986) in mice is insufficient to justify using a modifying factor for the protection of the fetus in the derivation of MRLs for parathion. Also note that the mice were exposed by intraperitoneal injection, a non-relevant route of exposure.*

COMMENT: The Reviewer states the following regarding Section 2.4, **TOXICOKINETICS**: Tables 3-7 to 3-9 need information on the time frame between exposure and measurement.

RESPONSE: *The requested information was added to the title of the tables.*

COMMENT: The following charge question was posed to the Reviewer: *Have all applicable metabolic parameters been presented?* The Reviewer responded: “Additional information on PON1 and variability by age and implications for metabolism needed. See references above.”

RESPONSE: *Relevant information has been added to Section 3.10, **SUSCEPTIBLE POPULATIONS**.*

COMMENT: The Reviewer noted that Figure 3-3 does not show a role for PON1.

RESPONSE: *PON1 has been included in Figure 3-3.*

COMMENT: The Reviewer had the following comment regarding Section 3.7, **CHILDREN’S SUSCEPTIBILITY**: “See embedded comments and comments above. Especially note PON1 work from our group, references above. Also, interesting discussion about toxicokinetics and possible dose differences during pregnancy. Recommend that MRLs consider FQPA type safety factor.”

RESPONSE: *All of these issues have been addressed in responses to comments above.*

COMMENT: The Reviewer had the following comment regarding Section 3.8, **BIOMARKERS OF EXPOSURE AND EFFECT**: “Minimal comments embedded in text. Note comments about PNP as an exposure metric for population studies.”

RESPONSE: *It is clearly stated in Section 3.8.1, **Biomarkers Used to Identify or Quantify Exposure to Parathion**, that p-nitrophenol is not a specific marker for parathion exposure (“However, it should be noted that p-nitrophenol can also be derived from exposure to methyl parathion, O-ethyl O-4-nitrophenyl phenylphosphonothioate (EPN), and other non-pesticide chemicals.”)*

COMMENT: The Reviewer stated the following regarding Section 3.9, **INTERACTIONS WITH OTHER CHEMICALS**: “Some discussion should be included that addresses the potential for co-exposure with other pesticides with the same mechanism of toxicity. The potential for exposure to parathion and other OP pesticides is likely limited to hazardous waste sites with multiple pesticide contaminants. To the extent information is available for the 21 hazardous waste sites with parathion present, a cross-tab can be run to determine if multiple OP pesticide exposure is possible. The U.S. EPA has provided guidelines on cumulative exposures and risk assessment to multiple OP pesticides. That information should be considered and referenced if warranted.”

RESPONSE: *It is unclear why the Reviewer feels that a discussion of possible interactions of parathion with other OP pesticides found in waste sites is necessary. Parathion, in the 21 waste sites where it has been found, has the potential to interact not only with other OP pesticides but also with other types of pesticides, and non-pesticide substances present in any given site. It seems beyond the scope of the section to discuss multiple potential interactions. The Reviewer is correct in that the U.S. EPA has*

provided guidelines on cumulative exposures and risk assessment to multiple OP pesticides (EPA 2006). That document is cited numerous times throughout the profile and was used to support the use of red blood cell acetylcholinesterase inhibition in intermediate-duration studies for derivation of MRLs for parathion. It should be noted, however, that parathion was not among the OPs included in EPA's cumulative risk assessment. No revisions were made.

COMMENT: The Reviewer stated the following regarding Section 3.10, **POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE**: “See discussion above and references addressing paraoxonase. Newborns and populations with specific polymorphisms are likely to have much lower PON1 activity and are likely more vulnerable to OP pesticides. This information should be considered with respect to safety factors and the need for the FQPA child safety factor.”

RESPONSE: *All of these issues have been addressed before. The following is the response to GENERAL COMMENT 10, above:*

FQPA safety factors are not among the standard uncertainty factors used by ATSDR. However, if there were compelling evidence indicating that young children might be more vulnerable to the effects of parathion (i.e., due to lower PON1 activity), ATSDR would consider using a modifying factor to adjust an MRL appropriately. Information regarding PON1 is provided in Section 3.10, POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE, taken from the recent review by Costa et al. (2013). The section has been expanded with information about PON1 activity being developmentally regulated. The following is part of the text that has been added: “Human studies have shown that PON1 activity is very low at birth and increases over time reaching a plateau between 6 months and a few years of age. There are also data indicating that PON1 activity may be even lower before birth as determined in premature babies compared to term babies. While this suggests that fetuses and young children may be at higher risk of organophosphate toxicity, it may not be the case regarding parathion based on data from studies with rat liver microsomes and human liver microsomes that have suggested that PON1 is not functionally important at the toxicologically relevant concentrations of paraoxon (Chambers et al. 1994; Mutch et al. 1999).”

Based on the data suggesting that PON1 is not functionally important at the toxicologically relevant concentrations of paraoxon, the fact that there was not significant exposure to parathion (if any) in the subjects studied in the papers listed by the Reviewer (exposure was mostly to chlorpyrifos, diazinon, malathion, and oxydemeton-methyl according to Bouchard et al. 2011), and that the profile is about parathion, ATSDR believes unnecessary to include in the profile information from the papers listed by the Reviewer.

COMMENT: Regarding the additional instructions: *Please review existing MRLs (intermediate inhalation and oral) for parathion and advise as to whether these values can also serve as guidance values for chronic inhalation and oral exposures for parathion? The MRL workgroup has recommended that we do not adopt the intermediate duration MRL for the chronic MRL - please advise.* The Reviewer commented: “I agree with the MRL workgroup in this and other related recommendations.”

RESPONSE: *No revisions were suggested.*

COMMENTS IN ANNOTATED PAGES ONLY

COMMENT: The comment refers to a statement indicating that no information was located regarding reproductive, developmental, or cancer effects in humans or animals following inhalation exposure to parathion. The Reviewer asks how this lack of information affects the MRL/RISK.

RESPONSE: *Lack of information on reproductive, developmental, and cancer by the inhalation route of exposure should not affect the MRL. Inspection of the oral database, which is more complete than the inhalation database, does not suggest that the end points in question are particularly sensitive to parathion toxicity. The available oral studies still suggested that the nervous system is the most sensitive target for parathion toxicity. There is no reason to assume that inhalation exposure will result in increased susceptibility for reproductive, developmental, or cancer effects relative to neurological effects.*

COMMENT: The comment refers to the following text in Section 3.2.2.3, **Immunological and Lymphoreticular Effects**: Studies in mice have also shown that pretreatment with 0.4 mg parathion/kg/day (the lowest dose tested) for 5 days increased the response to allergens such as 2,4-D-butyl and eugenol (Fukuyama et al. 2010). Both agents were classified as moderate sensitizers after pretreatment with vehicle, corn oil, and as strong sensitizers after pretreatment with parathion. In a subsequent study, the same group of investigators showed that pretreatment with parathion (0.15 mg/kg/day, the lowest dose tested) aggravated T_H1- and T_H2-type allergy (Fukuyama et al. 2011). According to the investigators, the mechanism for these effects may involve alterations in the number of helper and cytotoxic T-cells, in levels of T_H1 and T_H2 cytokines, and in gene expression in lymph nodes. The Reviewer asks to discuss the implications of T_H1/T_H2 ratios.

RESPONSE: *The following discussion was added: “Since T_H1- and T_H2-helper cells direct different immune pathways, alteration of their normal ratio may result in an unbalanced immune response to a challenge. Excessive proinflammatory responses due to overactivation of T_H1-type cytokines may lead to uncontrolled tissue damage, whereas excess T_H-2 responses will counteract the T_H-1-mediated microbicidal action.”*

COMMENT: The comment refers to a paragraph that describes two cases of organophosphorus pesticide-induced delayed neuropathy (OPIDN) attributed to acute intoxication with parathion. The Reviewer asks to discuss this information in relation to children development.

RESPONSE: *Neither one of the cases of OPIDN attributed to exposure to parathion occurred in children. It is unclear what exactly the Reviewer’s point is. No revisions were made.*

COMMENT: The comment refers to the summary of a cancer study in agricultural workers by Dennis et al. (2010) in Section 3.2.3.7, **Cancer**. The Reviewer suggested adding a conclusion at the end of the summary.

RESPONSE: *The following conclusion was added: “Overall, the study could not rule out the possibility that cutaneous melanoma was caused by exposure to arsenical pesticides. The investigators suggested that more research is needed regarding chemicals and other environmental factors that may increase the risk of cutaneous melanoma.”*

COMMENT: The comment refers to a paragraph in Section 3.5.2, **Mechanisms of Toxicity**, that summarizes the results of studies conducted by Slotkin and coworkers in neonatal rats administered parathion by subcutaneous injection. The Reviewer asks to discuss the findings in terms of susceptibility of children compared to adults.

RESPONSE: *The Reviewer's comment is vague and without further elaboration, it is difficult to determine what specific points she wants discussed based on Slotkin's results. Nevertheless, the following paragraph was added to Section 3.7, CHILDREN'S SUSCEPTIBILITY: "As previously mention in Section 3.2.4, Other Routes of Exposure (see that Section for references), a series of studies in which neonatal rats were administered subcutaneous doses of parathion that did not induce significant inhibition of AChE reported alterations in the development of neurotransmitter systems and metabolic dysregulation that were evident at later times up to adulthood. Since the various organophosphorus pesticides tested seemed to induce effects of opposing direction, the investigators suggested that organophosphorus pesticides can affect the developing nervous system via mechanisms not directly related to AChE inhibition."*

COMMENT: Referring to the Adequacy of the Database section, the Reviewer notes that future research to assess the potential for parathion exposure due to contaminated hazardous waste sites is a priority. Such research would be of low priority given the small amounts of parathion currently used and minimal exposure potential, unless the research is shown to provide useful information for the evaluation of other pesticides and chemicals.

RESPONSE: Research on the potential for parathion exposure due to contaminated hazardous waste sites was added to the profile in Section 6.8.1, *Identification of Data Needs*.

COMMENT: Referring to the Identification of Data Needs section, the Reviewer notes that future research to assess the potential for parathion exposure due to contaminated hazardous waste sites is a priority. Such research would be of low priority given the small amounts of parathion currently used and minimal exposure potential, unless the research is shown to provide useful information for the evaluation of other pesticides and chemicals.

RESPONSE: *Research on the potential for parathion exposure due to contaminated hazardous waste sites was added to the profile in Section 6.8.1, Identification of Data Needs.*

COMMENT: With regard to Chapter 4: Chemical and Physical Information, the Reviewer has no comment.

RESPONSE: *No revisions were suggested.*

COMMENT: With regard to Chapter 5: Production, Import/Export, Use, and Disposal, the Reviewer makes note of California PUR data.

RESPONSE: *Revisions were made as previously noted in response to General Comment 2.*

COMMENT: With regard to Chapter 6: Potential for Human Exposure, the Reviewer states that a section should be devoted to more recent and relevant exposure data. The Reviewer also states that the potential for exposure at hazardous waste sites with parathion should be described.

RESPONSE: *Revisions were made as previously noted in GENERAL COMMENTS 1 and 5.*

Comments provided by Reviewer #3

COMMENT: The comment refers to the question **What about birth defects** in Chapter 1, **PUBLIC HEALTH STATEMENT FOR PARATHION**. The Reviewer stated the following: “It is important to acknowledge the limits of just assessing morphometric aspects of birth defects. Functional impairment such as behavioral dysfunction need to be considered, especially given the target of parathion inhibiting acetylcholinesterase the catabolic enzyme for the important neurotransmitter acetylcholine. Research with developmental exposure of experimental animals to a variety of OP pesticides including parathion has shown lasting neurobehavioral impairment.”

RESPONSE: *Chapter 1 follows a standard profile format which includes the question about birth defects. If there had been studies reporting neurobehavioral alterations in children after gestational exposure to parathion they would have been mentioned in the paragraph under **Exposure effects for children generally**. Lasting neurobehavioral impairment has been shown in the studies by Slotkin and coworkers (Section 3.2.4, **Other Routes of Exposure**) in which neonatal rats were dosed with parathion and other organophosphorus pesticides by subcutaneous injection, a non-relevant route of exposure. As a result of comments from another Reviewer, the following paragraph was added to the section regarding children and parathion: “More recent studies of other similar pesticides found that long-term exposure might result in neurological problems in children (Bouchard et al. 2011; Eskenazi et al. 2007; Rauh et al. 2011). However, although parathion is in the same class as these other pesticides, it has not been directly implicated in the neurological alterations reported in these or other studies of children.”*

COMMENT: The comment refers to the following paragraph: “To prevent exposure and risk to the general population, the EPA terminated the production of end use product of parathion as of December, 2002 (EPA 2000). The EPA also terminated the last registration for parathion products effective on December 21, 2006 (EPA 2006a). Because of these actions and environmental degradation processes, it is likely that neither the general population nor workers are exposed to parathion in the United States.” The Reviewer’s comment is the following: Parathion is no longer use legally in this country. What about imports of food and other materials from other countries where it is still legal? What of illegal use?

RESPONSE: *It is possible that food items imported from countries where parathion is still used may be contaminated with the pesticide. As shown in Table 6-3, parathion was detected in various foods in surveys conducted from 1994 to 2000 (EPA 2002). In EPA’s 2006 Organophosphorus Cumulative Risk Assessment, parathion was not included among the 50 pesticides evaluated because of its negligible contribution to food, water, and residential exposure. Illegal use is always possible. No revisions were made.*

COMMENT: The comment refers to the following sentence in Section 2.2, **SUMMARY OF HEALTH EFFECTS**: “Almost all of the systemic effects observed following exposure to parathion are due to the action of its active metabolite, paraoxon, on the nervous system, or are secondary to this primary action.” The Reviewer’s comment is the following: “Almost all” is too definite a phrase. A more accurate phrase would be With the current state of knowledge the great majority of”. This would acknowledge both the instances of effects of parathion itself having biologic actions and the incompleteness of our knowledge about possible multiple mechanisms of actions of parathion. Other mechanisms of action beside the oxon inhibiting AChE have been found for other OPs.”

RESPONSE: *The text was revised as suggested.*

COMMENT: The comment refers to the following sentence: “Results from the AHS also showed no significant association between exposure to parathion and wheezing (Hoppin et al. 2006), non-allergic asthma (Hoppin et al. 2009), and behavioral function (Starks et al. 2012).” The Reviewer states that behavioral function is too vague and needs to be specified.

RESPONSE: *The sentence was revised as follows: “Results from the AHS also showed no significant association between exposure to parathion and wheezing (Hoppin et al. 2006), non-allergic asthma (Hoppin et al. 2009), and neurobehavioral function (memory, motor speed and coordination, sustained attention, verbal learning and visual scanning and processing) (Starks et al. 2012).”*

COMMENT: The Reviewer states that the developmental neurobehavioral studies by Slotkin and coworkers need to be discussed in Section 2.2, **SUMMARY OF HEALTH EFFECTS**.

RESPONSE: *The following sentence was added: “A series of studies in which neonatal rats were administered subcutaneous doses of parathion that did not induce significant inhibition of AChE reported alterations in the development of neurotransmitter systems and metabolic dysregulation that were evident at later times up to adulthood (Lassiter et al. 2010; Slotkin 2011; Slotkin et al. 2006a, 2006b, 2008, 2009a, Slotkin et al. 2009b, 2009c; Lassiter et al. 2010; Slotkin 2011).”*

COMMENT: The Reviewer states that developmental neurobehavioral papers by Timofeeva et al. (2008) and Levin et al. (2010) need to be added to the profile. The Reviewer provided copies.

RESPONSE: *The two papers mentioned by the Reviewer were added to the sections where the Slotkin studies are discussed.*

COMMENT: The Reviewer states the following regarding page 15, lines 18-21: “A study with an apparent lack of dose responsivity is cited. The term dose-responsivity is not used in a comprehensive manner. The means presents do not support a monotonic dose response but there are certainly examples of non-monotonic dose response functions, which could be the case here. However without indications of variability of the response, not just the means, it is impossible to make sense of these results. A toxicant exposure that causes infrequent but important effects can produce such a scattered pattern of means in an underpowered study. The same issue goes for the time effect function studies referred to later in the paragraph. It is appropriate to be conservative and have a lower threshold value in the face of this uncertainty.”

RESPONSE: *No revisions were suggested.*

COMMENT: The Reviewer states the following regarding page 22, lines 18-19: ” While it is true that inhibition AChE is common to all organophosphate pesticides it is not the only mechanism of toxicity of OPs. This is critically important to keep in mind especially when comparing toxic effects of different OPs.”

RESPONSE: *Text in Section 3.5.2, Mechanisms of Toxicity, was revised to state that there also seems to be other mechanisms of toxicity.*

COMMENT: The Reviewer states the following regarding page 24, lines 5-9: “Oral and buccal exposure should also be considered in the agricultural setting since OPs inhaled can be deposited in the oral mucosa and either directly absorbed or swallowed.”

RESPONSE: *The Reviewer’s suggestion was incorporated to the text.*

COMMENT: The Reviewer states the following regarding page 25, lines 4-8: “When evaluating negative effects inhaled aerosols on respiratory function in rodents it is important to remember that as obligate nose breathers rats have a different deposition pattern than humans.”

RESPONSE: *It is understood that rats are obligate nose breathers, but this should not be an issue. Methodology was developed by EPA to account for anatomical differences between rodents and humans in the derivation of benchmark values. That methodology would have been applied to estimate a human equivalent concentration in the derivation of the intermediate-duration inhalation MRL if particle size data had been available. No revisions were made.*

COMMENT: The Reviewer states the following regarding a paragraph that summarizes data from Hartwell et al. (1964) and provides temperatures in degrees Fahrenheit: “It is recommended that here and throughout the report that temperatures be reported in metric C as well as F.”

RESPONSE: *The corresponding temperatures in °C were added.*

COMMENT: The Reviewer stated the following: “In general with neurological effects it is important to consider receptor adaptation with chronic exposure. Tolerance can develop with longer exposure particularly as muscarinic cholinergic receptors down-regulate. This can in turn lead to effects as the OP is withdrawn. Considering this and other forms of neural adaptation, intermittent exposure can have more pronounced effects than continuous exposure because with intermittent exposure neural adaptation is more often inappropriate for the current level of exposure.”

RESPONSE: *No revisions were suggested.*

COMMENT: Regarding page 40, lines 23-25, the Reviewer has the following COMMENT: “It is confusing that it is said that 6 mg/kg of parathion blocked learning and memory but that memory was not significantly affected. Please clarify.”

RESPONSE: *The text was revised as follows: “In male Swiss-Webster mice, administration of a single gavage dose of 6 mg parathion/kg (only dose tested) blocked learning of a one-trial passive avoidance task, but did not significantly affect memory (Reiter et al. 1973).”*

COMMENT: The Reviewer had the following COMMENT: “Wording is important here. It should be stated that no significant embryotoxic or teratogenic to rabbits were found under the conditions of the study and that no significant maternal toxicity was found rather than that parathion was not embryotoxic or teratogenic to rabbits under the conditions of the study. No maternal toxicity occurred in the rabbits.”

RESPONSE: *The text was revised as follows: “Evaluation of the same end points examined in rats showed no significant embryotoxic or teratogenic effects in rabbits under the conditions of the study. No significant maternal toxicity occurred in the rabbits.”*

COMMENT: The Reviewer had the following comment regarding page 51 lines 7-10: “In addition to the possibility of a large number of statistical comparisons (Was there a correction such as Bonferroni to adjust alpha levels for multiple tests?), the results might be related to the findings that modest reduction in AChE activity is used for improvement of cognitive function in people with Alzheimer’s disease where AChE inhibitors are used therapeutically. This is a notable case in which there is a non-monotonic dose effect function.”

RESPONSE: *The comment seems to refer to text that summarizes the results of Stark et al. (2012), which showed that parathion exposure was associated with improved performance in some neurobehavioral tests performed by a group of elderly men. The answer to the Reviewer’s question is that Stark et al. (2012) did not specifically indicate whether a correction such as Bonferroni to adjust alpha levels for multiple tests was used. A sentence was added in the text stating that the possibility that a non-monotonic dose-effect function could not be ruled out.*

COMMENT: The Reviewer states that an article by Lee et al. (2013) regarding Parkinson’s disease and PON1 polymorphisms should be added to the profile.

RESPONSE: *The following information from Lee et al. (2013) was added: “In a more recent study, the same group of investigators examined whether single nucleotide polymorphisms PON1_{Q192R} and PON1_{C-108T} impact the association between Parkinson’s disease and residential exposure to parathion (Lee et al. 2013). PON1_{Q192R} affects catalytic efficiency of PON1, whereas PON1_{C-108T} has been associated with lower expression levels. The results of the analyses showed no significant increased risk associated with the variant genotypes studied (effect estimated included the null).”*

COMMENT: The Reviewer had the following comment regarding Section 3.2.3.6, **Developmental Effects:** “In the developmental effects section it would be important to add the more recent findings of the UC Berkeley and Columbia University groups on the epidemiology of OP exposure and cognitive development. As written, this section does not convey the extent of the epidemiological findings of developmental OP exposure impacts on cognitive function in children.”

RESPONSE: *Since the profile is about parathion and there was no significant exposure to parathion in the agricultural and residential populations studied by the UC Berkeley and Columbia University groups. The agricultural populations were exposed mostly to chlorpyrifos, diazinon, malathion, and oxydemeton-methyl according to Bouchard et al. (2011). The studies by the Columbia University concerned mainly chlorpyrifos. In addition, based on the data suggesting that PON1 is not functionally important at the toxicologically relevant concentrations of paraoxon, it is beyond the scope of the profile for parathion to include the findings of the studies suggested by the Reviewer. The following text was added to Chapter 1: “More recent studies of other similar pesticides found that long-term exposure might result in neurological problems in children (Bouchard et al. 2011; Eskenazi et al. 2007; Rauh et al. 2011). However, although parathion is in the same class as these other pesticides, it has not been directly implicated in the neurological alterations reported in these or other studies of children.”*

COMMENT: The Reviewer states the following apparently referring to Section 3.2.4, Other Routes of Exposure: “It would be important to note that the first week postnatal in the rat corresponds to the last trimester prenatally in the human in which the fetus receives parathion exposure via capillary bloodstream exchange with the mother across the placenta. This SC exposure via the capillary bed exposure is a reasonable model.” The Reviewer further states the following: “This would be the correct section to review the long-lasting neurobehavioral consequences of developmental parathion exposure in rats done in collaboration with the Slotkin group. Particularly relevant are the sex selective and age selective effective. See articles attached Timofeeva et al. (2008), Levin et al. (2010).”

RESPONSE: *The most relevant route of exposure to parathion in the past was via ingestion of foods contaminated with small residues of parathion. Subcutaneous injection is not an environmentally-relevant route of exposure. As noted by Slotkin et al. (2006a): “Parathion undergoes extremely high-first pass removal by the liver, reducing its oral bioavailability by more than 95% in the adult (Kramer and Ho 2002).” This means that in humans there is a safety mechanism by which most parathion is removed from circulation before reaches other tissues unless there is exposure to a very high amount of parathion. This section does summarize the studies by the Slotkin group and a sentence was added regarding the findings of Levin et al. (2010) and Timofeeva et al. (2008).*

COMMENT: The Reviewer had the following comment in reference to page 80, Section 3.4.3, **Metabolism:** “There should be an enhanced section on how genotype differences controlling metabolism of parathion affect kinetics. This should also be incorporated in the PBPK models discussed later.”

RESPONSE: *Information regarding PON1 and cytochrome CYP3A4 (the main human cytochrome involved in the metabolism of parathion) polymorphisms is presented in Section 3.10, **SUSCEPTIBLE POPULATIONS**. As mentioned before, studies with rat and human liver microsomes have suggested that PON1 is not functionally important at the toxicologically relevant concentrations of paraoxon. Therefore, while PON1 polymorphism may play an important role in the metabolism of chlorpyrifos or diazinon, it is not as relevant for parathion. Data from Gentry et al (2002) regarding incorporating polymorphism data into a PBPK model to assess variability in paraoxon tissue dose were added to Section 3.4.5, **Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models**.*

COMMENT: The Reviewer had the following comment regarding page 8, lines 1-11 (it appears that it may refer to Section 3.5.2, Mechanisms of Toxicity): “For the behavioral consequences of these low dose parathion effects see Timofeeva et al. (2008) and Levin et al. (2010) cited above.”

RESPONSE: *Timofeeva et al. (2008) and Lavin et al. (2010) have been added to all sections that discuss the Slotkin and coworkers studies.*

COMMENT: The following comment refers to Section 3.7, **CHILDREN’S SUSCEPTIBILITY:** “After extensive discussion about how children are not just small adults and react differently than adults to a variety of toxicants including parathion, it is strange that the statement is made that Parathion affects children in the same manner as it affects adults. This should be modified to state that in some ways they do but in other ways they react differently.”

RESPONSE: *The text about children not being just small adults is part of the boilerplate text that is included in every profile. The text about how parathion affects children now read as follows: “**Acute parathion exposure** affects children in the same manner as it affects adults. Regardless of the route of*

exposure, children exposed to high amounts of parathion exhibit the typical cholinergic signs and symptoms described in previous sections.”

COMMENT: The following comment seems to refer to a paragraph in Section 3.7, CHILDREN’S SUSCEPTIBILITY, summarizing the findings of Eskenazi et al. (2004) regarding parathion and developmental effects in children in an agricultural community in California: “However, the broader array of epidemiological studies concerning OP exposure during development do find significant associations with neurocognitive impairment. Given similarities in principal mechanisms of effect these should at least be mentioned.”

RESPONSE: *ATSDR would like to reiterate that the profile is about parathion. The lack of epidemiological studies dealing specifically with parathion is mentioned in Section 3.12.2, **Identification of Data Needs**.*

COMMENT: The Reviewer had the following comment regarding page 102, lines 31-34: “This would be a good section to address sex differences in response.”

RESPONSE: *Although pagination has changed, it seems that the comment refers to Section 3.10, **POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE**. Information regarding sex-related differences in oral LD₅₀ values in rats was added to this section. No other relevant data regarding sex differences in responses to parathion in animals or humans were located.*

COMMENT: The Reviewer had the following comment presumably regarding Section 3.9, **INTERACTIONS WITH OTHER CHEMICALS**: “Co-exposure to a high sugar diet could also exacerbate the obesity found by Lassitter et al. cited earlier.”

RESPONSE: *More relevant than the Lassiter studies seem studies by Olivier et al. (2001) and Liu et al. (2005, 2007) that suggested that people who consume excessive amount of sugar may be at a higher risk from exposure to parathion based on the results of studies in rats. This is discussed in section 3.10, **POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE**.*

COMMENT: The Reviewer had the following comment regarding Section 3.11.3, **Interfering with the Mechanism of Action for Toxic Effects**: “In addition to the muscarinic antagonist atropine, which would attenuate overstimulation of muscarinic cholinergic receptors, the nicotinic antagonist mecamylamine could be used to reduce overstimulation of nicotinic cholinergic receptors.”

RESPONSE: *While the use of a nicotinic antagonist seems intuitively correct, none of the toxicology books consulted and listed at the beginning of the section mention the use of a nicotinic antagonist in the management of organophosphorus pesticide poisoning. However, results from a study that showed that combined treatment of rats with paraoxon, atropine, and mecamylamine resulted in less adverse effects than treatment with paraoxon combined with either one of the acetylcholine antagonists were added to the text.*

COMMENT: The Reviewer stated the following regarding Section 3.12.2, **Identification of Data Needs**: “A broader array of epidemiological studies of OP pesticide exposure and associated impairments of development should be cited given similarities in mechanisms of actions.”

RESPONSE: Text was added to the **Developmental Toxicity** subsection in Section 3.12.2 stating that studies of pesticides with similar mechanisms of action have reported neurodevelopmental alterations in children following maternal exposure to those pesticides.

COMMENT: The Reviewer stated the following: “Animal studies have been conducted to determine the developmental neurobehavioral toxicity of parathion. These could be expanded.”

RESPONSE: The studies by Slotkin and coworkers have been acknowledged at the end of subsection **Neurotoxicity** in Section 3.12.2.

COMMENT: The Reviewer had the following general recommendation: “There should be greater coverage of the comparative effects of parathion and other OP pesticides. This would provide relative risk information and broaden the literature base when similar mechanisms of toxicity are known. Also, combined exposures of parathion and other OPs are likely to produce at least additive effects”

RESPONSE: The toxicological profile is not intended to discuss comparative effects of parathion and other organophosphorus pesticides.

COMMENT: The Reviewer had the following general recommendation: “There should be greater coverage of the long-term persisting effects of developmental parathion exposure. See Levin et al (2010). Parathion is no longer in legal use, but the long-term effects of developmental exposure are still being played in the population and need to be investigated so that we can know how to best deal with these persisting impairments. In addition new exposures can still occur with imports from countries where it is still used, illegal use in this country and exposure from dump sites.”

RESPONSE: The studies by Slotkin and coworkers have been given appropriate coverage considering the animals were exposed by subcutaneous injection, a non-relevant route of exposure. A statement was added to the Data Needs section suggesting that parathion be included in epidemiological studies monitoring developmental effects in children currently in progress.

COMMENT: Charge question: *Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Are there any general issues relevant to child health that have not been discussed in the profile and should be?* The Reviewer responded: “Long-term persisting effects and sex differences in response are not well covered. See recommendations detailed above”

RESPONSE: Studies that examined long-term persistent effects and sex differences were given appropriate coverage considering that the animals were treated by subcutaneous injection, a non-relevant route of exposure.

COMMENT: Charge question: *The tone of the chapter should be factual rather than judgmental. Does the chapter present the important information in a non-technical style suitable for the average citizen? If not, suggest alternate wording.* The Reviewer responded: “In general, the writing is factual and well presented. Since there is so much information presented additional executive summary information could be presented at the beginning.”

RESPONSE: *ATSDR will consider the suggestion of an executive summary for future profiles.*

COMMENT: Charge questions: *Major headings are stated as a question. In your opinion, do the answers to the questions adequately address the concerns of the lay public? Are these summary statements consistent, and are they supported by the technical discussion in the remainder of the text? Please note sections that are weak and suggest ways to improve them.* The Reviewer responded: “The report is pretty complete. Specific suggestions for improvement are listed above with page and line number.”

RESPONSE: *Please see the responses to the specific suggestions.*

COMMENT: Charge question: *Are scientific terms used that are too technical or that require additional explanation? Please note such terms and suggest alternate wording.* The Reviewer responded: “I think this is fine”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Do you agree with those effects known to occur in humans as reported in the text? If not, provide a copy of additional references you would cite and indicate where (in the text) these references should be included.* The Reviewer responded: “Comparison of parathion effects should be compared with those of other OPs to provide relative risk information and to provide a broader literature base where mechanisms of toxicity are similar.”

RESPONSE: *The toxicological profile is not intended to discuss comparative effects of parathion and other organophosphorus pesticides.*

COMMENT: Charge questions: *Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.* The Reviewer responded: “Yes, the animal model data are quite informative to human risk. Additions to this are suggested in the specific comments above.”

RESPONSE: *Please see responses to specific comments above.*

COMMENT: Charge question: *Have exposure conditions been adequately described? If you do not agree, please explain.* The Reviewer responded: “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? If not, were the major limitations of the studies sufficiently described in the text without providing detailed discussions. If study limitations were not adequately addressed,*

please suggest appropriate changes. The Reviewer responded: “The human studies presented were adequately described, but some comparisons should be made to other OPs.”

RESPONSE: *The toxicological profile is not intended to discuss comparative effects of parathion and other organophosphorus pesticides.*

COMMENT: Charge question: *Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the profile?* The Reviewer responded: “Yes”.

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Were all appropriate NOAELs and/or LOAELs identified for each study?* The Reviewer responded: “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Were the appropriate statistical tests used in the studies? Would other statistical tests have been more appropriate? Were statistical test results of study data evaluated properly?* The Reviewer responded: “Yes, as far as I could tell.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Are you aware of other studies which may be important in evaluating the toxicity of the substance?* The Reviewer responded: “No.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge questions: *Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study?* The Reviewer responded: “This was well covered.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Were the animal species appropriate for the most significant toxicological endpoint of the study?* The Reviewer responded: “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge questions: *Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the text? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)?* The Reviewer responded: “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Were all appropriate NOAELs and LOAELs identified for each study? Were all appropriate toxicological effects identified for the studies? If not, please explain.* The Reviewer responded: “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *If appropriate, is there a discussion of the toxicities of the various forms of the substance?* The Reviewer responded: “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge questions: *Were the appropriate statistical tests used in the interpretation of the studies? If not, which statistical tests would have been more appropriate? Were statistical test results of study data evaluated properly?* The Reviewer responded: “Yes, as far as I could tell.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge questions: *Are you aware of other studies that may be important in evaluating the toxicity of the substance? If you are citing a new reference, please provide a copy and indicate where (in the text) it should be included.* The Reviewer responded: “See the studies of Timofeeva et al., 2008 and Levin et al., 2010, attached. Their relevance and placement in the report are indicated in the specific comments above.”

RESPONSE: *Both studies were added to the appropriate sections.*

COMMENT: Charge question: *Are the LSE tables and figures complete and self-explanatory? Does the "Users Guide" explain clearly how to use them? Are exposure levels (units, dose) accurately presented for the route of exposure? Please offer suggestions to improve the effectiveness of the LSE tables and figures and the "User's Guide."* The Reviewer responded: “Fine, except that for temperature C as well as F should be given.”

RESPONSE: *Units of temperature do not appear in the LSE Tables or Figures, but °C were added to paragraph that mentioned °F.*

COMMENT: Charge question: *Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?* The Reviewer responded: “This seems OK.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *If MRLs have been derived, are the values justifiable? If no MRLs have been derived, do you agree that the data do not support such a derivation?* The Reviewer responded: “This seems well justified.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge questions: *Have the major limitations of the studies been adequately and accurately discussed? How might discussions be changed to improve or more accurately reflect the proper interpretation of the studies?* The Reviewer responded: “Mostly these are fine, some revisions are suggested in the specific comments above.”

RESPONSE: *See responses to specific comments above.*

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

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Have "bottom-line" statements been made regarding the relevance of the endpoint for human health?* The Reviewer responded: “Generally, this is OK except as noted in the specific comments.”

RESPONSE: *See responses to specific comment above.*

COMMENT: Charge question: *Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.* The Reviewer responded: “Yes.”

RESPONSE: *No revisions were suggested*

COMMENT: Charge question: *Has adequate attention been paid to dose-response relationships for both human and animal data?* The Reviewer responded: “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Has the animal data been used to draw support for any known human effects? If so, critique the validity of the support.* The Reviewer responded: “The comparisons are generally good. See specific comments above.”

RESPONSE: *See response to specific comments above.*

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

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Have the major organs, tissues, etc. in which the substance is stored been identified?* The Reviewer responded: “Yes.”

RESPONSE: *No revisions were suggested*

COMMENT: Charge question: *Have all applicable metabolic parameters been presented? Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented?* The Reviewer responded: “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Is there adequate discussion of the differences in toxicokinetics between humans and animals? What other observations should be made?* The Reviewer responded: “This is fairly complete.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Is there an adequate discussion of the relevance of animal toxicokinetic information for humans?* The Reviewer responded: “There is an issue with differences between rodent and human inhalation that should be discussed (See specific comments above.)”

RESPONSE: *See response to the specific comment above.*

COMMENT: Charge question: *If applicable, is there a discussion of the toxicokinetics of different forms of the substance.* The Reviewer responded: “NA.”

RESPONSE: *No revisions were made.*

COMMENT: Charge question: *Are the biomarkers of exposure specific for the substance or are they for a class of substances?* The Reviewer responded: “Both specific metabolites and nonspecific for the class AChEI.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Are there valid tests to measure the biomarker of exposure? Is this consistent with statements made in other sections of the text?* The Reviewer responded: “The coverage of this issue seems fine.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Are the biomarkers of effect specific for the substance or are they for a class of substances?* The Reviewer responded: “The effects are general across the class, AChEI, neurochemical changes and functional changes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Are there valid tests to measure the biomarker of effect? Is this consistent with statements made in other sections of the text?* The Reviewer responded: “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge questions: *Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? If not, please clarify and add additional references.* The Reviewer responded: “There should be additional coverage of comparison and interactions with other OPs.”

RESPONSE: *All the information available regarding interaction of parathion with other organophosphorus pesticides is in Section 3.9, **INTERACTIONS WITH OTHER CHEMICALS**.*

COMMENT: Charge question: *If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions?* The Reviewer responded: “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Is there a discussion of populations at higher risk because of biological differences which make them more susceptible?* The Reviewer responded: “Yes, these are well covered, except that additional coverage of the long-term effects of developmental exposure should be provided.”

RESPONSE: *Parathion has not been implicated in the neurodevelopmental effects in children reported in the studies of agricultural communities. The studies of Slotkin and coworkers in which rats are treated with parathion by subcutaneous injection are given appropriate coverage throughout the profile; a paragraph summarizing their findings was added to Section 3.10, **SUSCEPTIBLE POPULATIONS**.*

COMMENT: Charge question: *Is the management and treatment specific for the substance, or is it general for a class of substances?* The Reviewer responded: “There are some parathion specific aspects and some general to other OPs as is appropriate.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge questions: *Is there any controversy associated with the treatment? Is it a “well accepted” treatment?* The Reviewer responded: “The treatment is standard.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?* The Reviewer responded: "There may be risks associated with atropine treatment, but there would be greater risks of not treating people with high dose parathion exposure."

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Are treatments available to prevent the specific substance from reaching the target organ.* The Reviewer responded: "There is a treatment to counteract its effect."

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Is there any controversy associated with the treatment? Is it a "well-accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method?* The Reviewer responded: "Yes, this treatment is well accepted. I agree except that additional nicotinic antagonist treatment should be tested."

RESPONSE: *None of the toxicology books consulted recommended using a nicotinic antagonist. No changes were made.*

COMMENT: Charge question: *Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?* The Reviewer responded: "There may be hazards associated with atropine treatment but there would be greater hazards of not treating high dose parathion exposure."

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Are there treatments to prevent adverse effects as the substance is being eliminated from the major organs/tissues where it has been stored.* The Reviewer responded: "Not that I know of."

RESPONSE: *No revisions were suggested.*

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

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Is there any controversy associated with the treatment? Is it a "well-accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method?* The Reviewer responded: "Yes."

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?* The Reviewer responded: “There may be hazards associated with atropine treatment but there would be greater hazards of not treating high dose parathion exposure.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Do you know of other studies that may fill a data gap? If so, please provide the reference.* The Reviewer responded: “Yes, these references have been added.”

RESPONSE: *Information from the references suggested was added to the profile.*

COMMENT: Charge question: *Are the data needs presented in a neutral, non-judgmental fashion?* The Reviewer responded: “This is fine.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Do you agree with the identified data needs?* The Reviewer responded: “Yes, but some have been added as noted in the specific comments above.”

RESPONSE: *See responses to the specific comments above.*

COMMENT: Charge question: Does the text indicate whether any information on the data need exists?
Reviewer’s COMMENT: “Yes.”

RESPONSE: No revisions were suggested.

COMMENT: Charge question: *Does the text adequately justify why further development of the data need would be desirable; or, conversely, justify the “inappropriateness” of developing the data need at present?* The Reviewer responded: “Yes.”

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Are you aware of any information or values that are wrong or missing in the chemical and physical properties tables? Please provide appropriate references for your additions or changes.* The Reviewer responded: “Generally, this is fine. Some added refs are listed.”

RESPONSE: *The references suggested were added.*

COMMENT: Charge question: *Are you aware of any information that is wrong or missing?* The Reviewer responded: “Generally, this is fine. Some added refs are listed.”

RESPONSE: *The references suggested were added.*

COMMENT: Charge 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?* The Reviewer responded: *"This is fine."*

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.* The Reviewer responded: *"This is fine."*

RESPONSE: *No revisions were suggested.*

COMMENT: Charge 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?* The Reviewer responded: *"This is fine."*

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations?* The Reviewer responded: *"This is fine."*

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Are you aware of other regulations or guidelines that may be appropriate for the table?* The Reviewer responded: *"No."*

RESPONSE: *No revisions were suggested.*

COMMENT: Charge question: *Are there additional references that provide new data or are there better studies than those already in the text? If so, please provide a copy of each additional reference.* The Reviewer responded: *"These have been provided."*

RESPONSE: *The references suggested were added.*

COMMENT: Charge question: *For each of the unpublished studies included with the profile, prepare a brief evaluation that includes your assessment of the:
Adequacy of design, methodology, and reporting;
Validity of results and author's conclusions; and*

Study inadequacies or confounding factors.

Provide a summary of your conclusions? Do you agree or disagree with those of the author? If not please explain why. The Reviewer responded: “These are well reviewed in the report.”

RESPONSE: *No revisions were suggested.*

COMMENT: *Charge question: Please review existing MRLs (intermediate inhalation and oral) for parathion and advise as to whether these values can also serve as guidance values for chronic inhalation and oral exposures for parathion? The MRL workgroup has recommended that we do not adopt the intermediate duration MRL for the chronic MRL - please advise.* The Reviewer responded: “I agree. Chronic exposure by inhalation or oral routes may produce toxic effects that are not predicted by the intermediate-duration exposure. In addition, lack of inhibition of AChE does not mean lack of toxicity at that dose or duration as shown by the Slotkin studies.”

RESPONSE: *No revisions were suggested.*