

**Disposition of Peer Review Comments for
Toxicological Profile for JP-5, JP-8, and Jet A Fuels**

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

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Peer reviewers for the third pre-public comment draft of the Toxicological Profile for JP-5, JP-8, and Jet A Fuels were:

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Comments provided by Peer Reviewer #1:

General Comments

COMMENT 1: This is a complete review of what is known about the toxicity of jet fuels including Jet A, JP-8 and JP-5. Each of these materials are made up of complex and variable mixtures similar to kerosene in composition. Because these are mixtures refined from a variety of feed stocks jet fuels are highly variable in composition. In some instances kerosene is used as an analog especially in the case of childhood poisoning.

The exposed populations appear to be those persons conducting maintenance for turbine powered general, commercial and military aviation aircraft and some vehicles.

Effects are varied. Little data exists in humans and animal studies are the primary source of toxicological information. For several of the inhalation studies the measured amounts are likely to be an underestimate of the true exposure to the animals.

The use, number of contaminated sites and the fate and transport information is clear. Since jet fuel is a mixture of similar compounds and highly variable measurements of the typical constituents used to assess quantities and biodegradation.

The questions appear to be generic to the ATSDR review process. Jet fuels are complex mixtures and relatively limited in the scope of their use. Compared to many chemicals there is a rather limited database. There are few human studies and relatively few animal investigations. A few large studies constitute a major portion of the available data. The research conducted at the University of Arizona is such an example. Because of the similarity to kerosene those toxicity data are also used in certain circumstances. However jet fuels are more refined and must meet ASTM and other specifications.

RESPONSE 1: *No revisions were suggested.*

Charge Questions and Responses

CHAPTER 1 – PUBLIC HEALTH STATEMENT

QUESTION 1: 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.

COMMENT: I have found that the question and answer format works well for a number of audiences. I have some notes on specific items.

RESPONSE: *No revisions were suggested.*

QUESTION 2: 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.

COMMENT 2-1 (page 2, line 14): The paragraph is an excellent summary of the fate and transport of jet fuels.

RESPONSE 2-1: *No revisions were suggested.*

COMMENT 2-2 (page 6, line 25): The recommended limit of 100 mg/m³ probably does not mean much to the general public. Should a more detailed explanation be considered? Since jet fuel is a complex mixture it is not clear if this means the volatiles or the aerosols?

RESPONSE 2-2: *NIOSH did not specify whether the limit was for volatiles or aerosols.*

QUESTION 3: Are scientific terms used that are too technical or that require additional explanation?

COMMENT: See the note above regarding the units.

RESPONSE: *See Response to the previous comment.*

CHAPTER 2 – RELEVANCE TO PUBLIC HEALTH

QUESTION 1: Do you agree with those effects known to occur in humans as reported in the text?

COMMENT: Yes but there are very little data on effects on humans. Most of the data deal with animals.

RESPONSE: *No revisions were suggested.*

QUESTION 2: Are the effects only observed in animals likely to be of concern to humans? Why or why not?

COMMENT: Most of the effects are found only in animals because of the lack of data for human exposures and effects. There are a number of uncertainty factors used because of this lack of information.

RESPONSE: *No revisions were suggested.*

QUESTION 3: Have exposure conditions been adequately described?

COMMENT 3-1 (page 9, lines 4-6): Yes, but I am frustrated by the lack of measurement specifics; exposure groups of 4.4 mg/m³, 0.9 mg.m³ and so on. However there are no standard deviations or other error terms are stated with the numbers.

RESPONSE 3-1: *It is beyond the scope of the profile to provide the standard deviations or standard errors of the mean for the actual exposure levels.*

COMMENT 3-2 (page 10 and the use of NOAEL): I am not sure if the typical reader understand that this is the result of a statistical test at a concentration chosen by the investigator. So these numbers are not a clear description of the exposure-response curve.

RESPONSE 3-2: *The intended audience for Chapter 2 is health assessors; ATSDR assumes that these users understand that identified NOAELs and LOAELs are reflective of the dose levels selected by the investigators.*

COMMENT 3-3 (page 17, line 17-18): Excellent policy on the use of free-standing NOAEL values.

RESPONSE 3-3: *No revisions were suggested.*

CHAPTER 3 –HEALTH EFFECTS

SECTION 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

Toxicity – Quality of Human Studies

QUESTION 1: 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?

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

QUESTION 2: 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)?

COMMENT: The text provides adequate justifications.

RESPONSE: *No revisions were suggested.*

QUESTION 3: 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?

COMMENT: NOAELs and LOAELs are well documented and the limitations are addressed. There are substantial limitations to the use of hypothesis testing to understanding thresholds and describing uncertainty in the exposure-response relationship. See note to next question.

RESPONSE: *No revisions were suggested.*

QUESTION 4: 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?

COMMENT: The use of NOAELs and LOAELs do not adequately describe the exposure-response curves derived from the various studies. Only in a few instances were LC50 or other endpoints derived from curve fitting (such a probit analysis) reported in the dataset. It is therefore very difficult to judge the inherent variability of the exposure-response information. I understand that many studies only report NOAELs or LOAELs but access to the original data should allow a reanalysis of the exposure-response relationships.

RESPONSE: *It is beyond the scope of the profile for ATSDR to model the exposure-response relationships for each study discussed in Section 3.2. The Agency has used the standard practice of reporting NOAEL and LOAEL values. ATSDR has used benchmark dose modeling of the critical effects for the derivation of MRLs.*

QUESTION 5: 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.

COMMENT: No

RESPONSE: *No revisions were suggested.*

Toxicity – Quality of Animal Studies

QUESTION 1: 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)?

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

QUESTION 2: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT: The species of rats, mice and so on are the typical animals used in these kinds of studies.

RESPONSE: *No revisions were suggested.*

QUESTION 3: 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)?

COMMENT: The specific criteria used by ATSDR prove adequate for evaluating the inclusion of the studies.

RESPONSE: *No revisions were suggested.*

QUESTION 4: Were all appropriate NOAELs and LOAELs identified for each study? Were all appropriate toxicological effects identified for the studies?

COMMENT: Please see the earlier note about the limitations of NOAELs and LOAELs in determining exposure-response. Page 28 line 17 provides an excellent example of the use of curve fitting. The RD50 is determined along with the confidence interval.

RESPONSE: *See the Response to Question 4 in the Quality of Human Studies section.*

QUESTION 5: If appropriate, is there a discussion of the toxicities of the various forms of the substance?

COMMENT: In the reviews it is not clear what the source of the jet fuel was. In my research we recorded the lot number of the JP-8 or JP-4 so original source could be identified. Since fuels from different feed stocks are known to be of slightly different chemical makeup identification may be useful.

RESPONSE: *Some of the cited studies provided information on the feedstocks for the jet fuels (batch numbers or source); this information was added to the supplemental document.*

QUESTION 6: Were the appropriate statistical tests used in the interpretation of the studies? If not, which statistical test would have been more appropriate? Were statistical test results of study data evaluated properly?

COMMENT: As stated in earlier answers there are alternatives to the use of hypothesis testing to derive exposure-response relationships.

RESPONSE: *See the Response to Question 4 in the Quality of Human Studies section.*

QUESTION 7: Are you aware of other studies which may be important in evaluating the toxicity of the substance?

COMMENT: No.

RESPONSE: *No revisions were suggested.*

Levels of Significant Exposure (LSE) Tables and Figures

QUESTION 1: Are the LSE tables and figures complete and self-explanatory? Does the “Users Guide” explain clearly how to use them? Are exposure levels (units and dose) accurately presented for the route of exposure?

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

QUESTION 2: Do you agree with the categorization of “less serious” or “serious” for the effects cited in the LSE tables?

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

QUESTION 3: 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?

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

Evaluation of Text

QUESTION 1: Have the major limitations of the studies been adequately and accurately discussed? How might discussion be changed to improve or more accurately reflect the proper interpretation of the studies?

COMMENT: The text is well written.

RESPONSE: *No revisions were suggested.*

QUESTION 2: Has the effect, or key endpoint, been critically evaluated for its relevance in both humans and animals?

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

QUESTION 3: Have “bottom-line” statements been made regarding the relevance of the endpoint for human health?

COMMENT: It is not exactly clear what is meant by this question. The results of the animals studies are discussed and are often used to determine suggested exposure limits. The limitations of these studies are apparent in the high uncertainty factors (totaling 100 in most cases) applied to the results.

RESPONSE: *No revisions were suggested.*

QUESTION 4: Are the conclusions appropriate given the overall database?

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

QUESTION 5: Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

COMMENT: Not clear to this reviewer. The dose-response has been described via the use of hypothesis testing in most instances (NOAELs and so on) with only a few cases of curve fitting being used. Because of this I would say that statistical thresholds have been described but the LD50 or RD50 (could easily be LD10 or LD20) with confidence intervals are not adequately described.

RESPONSE: *See Response to Question 4 in the Quality of Human Studies section.*

QUESTION 6: Has the animal data been used to draw support for any known human effects?

COMMENT: Again, because of the scarcity of the human data it is difficult to extrapolate from animal or bacteria studies (Ames assay) to human effects.

RESPONSE: *No revisions were suggested.*

SECTION 3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

QUESTION 1: Is there a discussion of populations at higher risk because of biological differences which make them more susceptible? Do you agree with the choices of populations? Why or why not? Are you aware of additional studies in this area?

COMMENT: There is a discussion of how poisoning of children with kerosene is very common in the third world. However, children are not the most likely population to have access to jet fuels.

RESPONSE: *The intent of this section is to identify populations that may be unusually susceptible to the toxicity of jet fuels. A discussion of populations with higher potential for exposure is included in Chapter 6.*

SECTION 3.11 METHOD FOR REDUCING TOXIC EFFECTS

General Discussion Regarding Treatments To Reduce Peak Absorption

QUESTION 1: Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?

COMMENT: None apparent from the available data.

RESPONSE: *No revisions were suggested.*

QUESTION 2: 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?

COMMENT: No.

RESPONSE: *No revisions were suggested.*

QUESTION 3: Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?

COMMENT: No.

RESPONSE: *No revisions were suggested.*

QUESTION 4: Are there any 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)?

COMMENT: No.

RESPONSE: *No revisions were suggested.*

Methods to Block the Mechanisms of Toxic Action

QUESTION 1: Are treatments available to prevent the specific substance from reaching the target organ(s), or are the actions general for a class of substances?

COMMENT: None apparent.

RESPONSE: *No revisions were suggested.*

QUESTION 2: 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?

COMMENT: None apparent.

RESPONSE: *No revisions were suggested.*

QUESTION 3: Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?

COMMENT: None apparent.

RESPONSE: *No revisions were suggested.*

SECTION 3.12 ADEQUACY OF THE DATABASE

Existing Information on Health Effects

QUESTION 1: Do you know of other studies that may fill a data gap? If so, please provide the reference.

COMMENT: No.

RESPONSE: *No revisions were suggested.*

Identification of Data Needs

QUESTION 1: Are the data needs presented in a neutral, non-judgemental fashion? Please note where the text shows bias.

COMMENT: The information is presented in a clear and unbiased manner. The authors were very careful to note the limitations of the case examples and of several of the studies. The organization of this section is very logical and clearly presented.

RESPONSE: *No revisions were suggested.*

QUESTION 2: Do you agree with the identified data needs? If not, please explain your response and support your conclusions with appropriate references.

COMMENT: I concur with the identified needs.

RESPONSE: *No revisions were suggested.*

QUESTION 3: Does the text indicate whether any information on the data need exists?

COMMENT: Section 3.12.3 discusses the data needs for several types of studies. The organization is very clear and there are numerous data needs described using the same organization in which the original results were presented. I really appreciate the parallel organization of these two sections. This section also addresses the issues covered in the next question.

RESPONSE: *No revisions were suggested.*

QUESTION 4: 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.

COMMENT: See answer above. I will use the organization of these sections as a model for similar reviews in the future.

RESPONSE: *No revisions were suggested.*

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

QUESTION 1: Are you aware of any information or values that are wrong or missing in the chemical and physical properties tables?

COMMENT: No, this chapter is a clear and extensive summary.

RESPONSE: *No revisions were suggested.*

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

QUESTION 1: 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?

COMMENT: The information appears as I would expect for jet fuels. The mechanisms for release to the environment are well known. In the case of the military it will be from former locations where storage for aviation and now turbines in tanks has occurred.

RESPONSE: *No revisions were suggested.*

QUESTION 2: 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?

COMMENT: The information is clearly presented and covers a variety of environmental media.

RESPONSE: *No revisions were suggested.*

QUESTION 3: 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?

COMMENT: The material in this section is well presented and appears complete.

RESPONSE: *No revisions were suggested.*

QUESTION 4: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high

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

COMMENT: The general population should not be exposed unless there is an emergency release of fuel or they visit an airfield (base) where the material is used. In some instances groundwater can also be contaminated.

Perhaps my biggest concern regarding exposure is for those maintainers cleaning the fuel bladders of KC-135 or KC-10 or similar tanker aircraft. Although the crews wear protective equipment failure of the respirator or clothing may lead to a high level of exposure.

RESPONSE: *The potential of high exposures in fuel tank maintenance workers is discussed in Section 6.7.*

Section 6.8.1 Identification of Data Needs and Section 6.8.2 Ongoing Studies

QUESTION 1: For Sections 6.8.1, Identification of Data Needs and 6.8.2, Ongoing Studies, answer the same questions presented in Section 3.12.2, Identification of Data Needs and 3.12.3, Ongoing Studies.

COMMENT: As in section 3.12.2 and 3.12.3 the presentation of data needs follows the organization of the exposure sections. The information is clearly presented. I agree with the presentation of the data needs for the estimation of exposure for contaminated sites.

RESPONSE: *No revisions were suggested.*

CHAPTER 7. ANALYTICAL METHODS

GENERAL COMMENT: My expertise is not that of an analytical chemist. However the methods presented in this section appear to be those typical for measuring jet fuels and their constituents.

RESPONSE: *No revisions were suggested.*

QUESTION 1: Are you aware of additional methods that can be added to the tables?

COMMENT: No.

RESPONSE: *No revisions were suggested.*

QUESTION 2: If unique issues related to sampling for the substance exist, have they been adequately addressed in the text? What other discussions should be provided?

COMMENT: The materials appear appropriate.

RESPONSE: *No revisions were suggested.*

CHAPTER 8. REGULATIONS AND ADVISORIES

QUESTION 1: Are you aware of other regulations and guidelines that may be appropriate for the table?

COMMENT: No, The regulations and guidelines look complete.

RESPONSE: *No revisions were suggested.*

CHAPTER 9. REFERENCES

QUESTION 1: Are there additional references that provide new data or are there better studies than those already in the text?

COMMENT: No.

RESPONSE: *No revisions were suggested.*

Review of Unpublished Studies

The Peer Reviewer reviewed the following unpublished studies and did not object to the inclusion of these studies in the profile.

Hurley JM, Wagner D, Sterner TR, et al. 2011. Acute Dermal Irritation Study of JP-8 and S-8 in New Zealand White Rabbits. [AFRL-RH-WP-TR-2011-0054].

Mattie DR, Cooper JR. 2001. Developmental Neurobehavioral Effects on JP-8 Jet Fuel on Pups from Female Sprague-Dawley Rats Exposed by Oral Gavage. [AFRL-HE-WP-TR-2001-0186].

Wagner MJ, Stevens SC, Guilfoil AJ, et al. 2009. Evaluation of Barrier Skin Cream Effectiveness Against JP-8 Jet Fuel Absorption and Irritation. [AFRL-RH-WP-TR-2009-0086].

Whitman FT, Hinz JP. 2004. Sensory Irritation Study in Mice: JP-5, JP-TS, JP-7, DFM, JP-10. [IOH-RS-BR-SR-2004-0001].

Mattie DR, Marit GB, Cooper JR, et al. 2000. Reproductive Effects of JP-8 Jet Fuel on Male and Female Sprague-Dawley Rats After Exposure by Oral Gavage. [AFRL-HE-WP-TR-2000-0067].

Comments provided by Peer Reviewer #2:

General Comments

COMMENT 1: I think the first chapter meets the needs to guide the lay public; however, I think the “Profile” should highlight some additional information, such as speaking about populations environmentally exposed, especially those living in the surroundings where use these fuels, which age group is most affected, or what is the sex with the greater proportion of effects from exposure to these jet fuels and give details of the other factors mentioned and even set some explanations, without speculation, and why is distributed in this or that way.

RESPONSE 1: *Potential sources for general population exposure to jet fuels is discussed in numerous sections of the profile including Chapter 1 (How Might I be Exposed to JP-5, JP-8, and Jet A Fuels), Section 2.1, and Section 6.5. ATSDR did not identify data that would support identifying a particular age group or sex that would be more likely to be environmentally exposed to jet fuels.*

COMMENT 2: I do not agree at all that chapters or sub-chapters of a manuscript be established as questions, but thinking that the content should attract the interest of the general public, and especially with those with some suspicions of exposure or already have a possible effect, I think it should be preserved as well.

RESPONSE 2: *Only Chapter 1 is divided into questions.*

COMMENT 3: In the 2nd paragraph on page 2, about the presence of certain chemicals in the jet fuels that can be detected in fish and aquatic organisms after an accidental spill, release into a lake, river, or stream, but mentioning this is very different with the accumulation of these chemicals in these organisms should be clarified. As described, it might be misunderstood or even perceived as a contradiction.

RESPONSE 3: *The text was revised to indicate that the jet fuel hydrocarbons are not likely to persist in aquatic organisms.*

COMMENT 4: I also think that in this chapter should be clarified that there are acute and chronic exposures, although later in the same manuscript, some clarifications are made.

RESPONSE 4: *The first sentence in the “How JP-5, JP-8, and Jet A fuels Can Affect Your Health?” section notes that the health effects can depend on how long you are exposed to the fuels.*

COMMENT 5: The question of "How Can Families Reduce the Risk of Exposure to JP-5, JP-8 and Jet A Fuels?" which appears on page 5, I think is not answered in the way that it is written. It even gives me the impression that the question should not appear.

RESPONSE 5: *A statement was added that workers exposed to jet fuels should change their clothes prior to leaving their job.*

COMMENT 6: Should not be convenient point out why there are still differences in the use of different exposure times referred in the second paragraph on page 6? (In the subchapter: What Recommendations Has the Federal Government Made to Protect Human Health?)

RESPONSE 6: *ATSDR believes that it would be very confusing to attempt to explain why different organizations use different exposure times. The intent of the statement is to let the reader know that there are differences.*

COMMENT 7 (Chapter 2): I agree with the effects listed, however, the best known and most studied or focused are the effects at the neurological level, should perhaps be described as the first and not start with respiratory effects. I think that the effects to describe, with the purposes to give some hierarchy, although they have been very little explored or less evident, the neurological effects are the most commonly identified in humans, and then all those effects who have had more relevance or evidence in animals.

RESPONSE 7: *The text was revised to include the discussion of neurotoxicity prior to the discussion of other effects.*

COMMENT 8: I understand that the text desires to point out the toxicological information in the first instance, but I think the subchapter "Summary of Health Effects" should be more balanced in terms that the chapter is called "Relevance in Public Health"; In other words: it seems that the "Profile" is more concerned with describing what has been found in animals than in humans.

RESPONSE 8: *There are limited reliable data on the toxicity of JP-5, JP-8, and Jet A fuels in humans; thus, the profile needs to rely of animal toxicity data in order to identify potential targets of toxicity and establish dose-response relationships.*

COMMENT 9: In addition to the previous point, I think it must somehow speak why the few information about the health effects on staff or workers who are occupationally exposed to jet fuels or population that is environmentally exposed because they live in the surroundings where this kind of fuels are used.

RESPONSE 9: *ATSDR is unable to speculate as to why there are limited data on occupationally or environmentally exposed individuals.*

COMMENT 10: Subchapter 2.1 (first paragraph on page 8) BACKGROUND AND ENVIRONMENTAL EXPOSURES TO JP-5, JP-8, JET A AND FUELS IN THE UNITED STATES, might be best noted as "Sources" and not as "Backgrounds".

RESPONSE 10: *ATSDR will consider the Reviewer's suggested title change in subsequent revisions of the toxicological profile guidance document.*

COMMENT 11: At the beginning of page 9, certain concentrations of various substances contained in jet fuels are mentioned, though not detailed which conclusions were reached. It seems important that those conclusions should be noted.

RESPONSE 11: *No conclusions can be reached regarding these concentrations primarily because the studies only examined a limited number of compounds.*

COMMENT 12: I think the chapter is very shallow in terms of Public Health; this should speak and expand information not only regarding the "magnitude" of the problem in the population, but of the "transcendence" of it, i.e., the social and health impacts because the production and use of jet fuels over the population or the society; besides, should also talk about the "vulnerability" of the problem and the "feasibility" of modifying it. I do not really see clearly these fundamental topics of Public Health. It should probably rename the section as is and not talk as "Relevance to Public Health."

RESPONSE 12: *It is beyond the scope of the profile to examine the social impacts of the use of jet fuels and feasibility of modifying the health effects. The intent of this section is to briefly describe the potential of exposure to jet fuels and the observed health effects.*

COMMENT 13: I think human studies will always have great limitations and, despite this, the manuscript makes an effort not only to deliver what results were obtained, but also discusses the limitations that faced their respective authors and considering that the results are turned into scientific nature evidence.

RESPONSE 13: *No revisions were suggested.*

COMMENT 14: I have no relevant comments about the NOAELs and LOAELs identified in each study.

RESPONSE 14: *No revisions were suggested.*

COMMENT 15: Discuss whether the statistical tests used were the most appropriate is hard to mark out because only with further information for each of the studies cited would enter into the critical analysis of whether the proposed tests were the best, so I agree with which states: "... the proper statistical Analyses Contribute to the reliability of the data...". I have to insist that with the provided information is very difficult to answer the point fully.

RESPONSE 15: *No revisions were suggested.*

COMMENT 16: Personally, I have little experience in animal studies design, so my limitation as to whether it was the right number of them for this or that study, the required and needed, causes of death or sufficient number of dose groups, if the animals specie was the adequate, and enough magnitude of dose levels. Nonetheless my limitations on required expertise in animal studies, it seems to me that the NOALs and LOALs identified and discussed are suitable enough for the format of a "Profile".

RESPONSE 16: *No revisions were suggested.*

COMMENT 17: As regards to the appropriate statistical tests applied, I think there is the same situation as noted above.

RESPONSE 17: *No revisions were suggested.*

COMMENT 18: I think the LSE tables and figures are sufficiently self-explanatory and the "Users Guide" is clear as to how they should be used, however, especially with the idea of improving it, would be worth an exploration of future users of this document if this really is true. Also how are stipulated the measurement units.

RESPONSE 18: *In general, ATSDR uses ppm units for inhalation studies involving vapors or gases and mg/m³ units for aerosols for the inhalation LSE tables and figures. For the oral LSE tables and figures, mg/kg body weight/day units are used. Because it is often not possible to use a single exposure measurement unit for dermal exposure studies, ATSDR uses the unit reported by the study investigators.*

COMMENT 19: Furthermore, the categorization of something as soft as "less serious" or "serious" will always be criticized, but I understand it's for better understanding or even for future decision making. I think the question of whether or not MRLs have been derived, deserve a more specific expert consensus, to not remain as a mere opinion.

RESPONSE 19: *MRLs presented in this toxicological review have undergone extensive review by ATSDR's Intra-agency and Interagency MRL Workgroups.*

COMMENT 20: I notice that quite often throughout the text of this "Profile", talks about limitations of the studies that have been conducted on the subject. Undoubtedly, any reference to it is best not to; besides, I also believe that any material, and this is no exception, it could be discussed at length, mainly because there are many knowledge gaps. One way to measure it, although very difficult, would be to know which of the studies referred to the "Profile" received a letter to the editor about it, or to what extent is quoted by other studies. This, of course, merit a very deep literature review.

RESPONSE 20: *In evaluating individual studies, ATSDR also evaluates letters to the editor (as well as the author's responses); if relevant issues are raised, they are discussed in the profile. ATSDR disagrees with the Reviewer that including information on the number of times a paper is cited by another study would provide useful information for the profile user.*

COMMENT 21: The "bottom line" statements are made regarding to the relevance of the endpoint for human health. It will always be difficult to talk about "conclusions", and it would be presumptuous of me to want to note other than those that the authors considered only as such. I think that would fall on too much speculation and it is well known that there are areas that remain and may remain for long time in uncertainty.

RESPONSE 21: *No revisions were suggested.*

COMMENT 22: There is adequate attention to the dose-response relationships for both humans and animals. I do not think any study has been made useless without interest to know how works in humans, that after all, is the goal of any toxicological study.

RESPONSE 22: *No revisions were suggested.*

COMMENT 23: I must insist that the current document is a "Profile" and not a compendium; in this sense it could be said that there is sufficient discussion of absorption, distribution, metabolism, and excretion of "X" substance. If there is interest in knowing more, the user definitely have to go to the particular study and make critical reading of it. The same could be said about the major organs or tissues in which the substance is stored.

RESPONSE 23: *No revisions were suggested.*

COMMENT 24: I think the presented material is adequate or at least be sure that you have at hand the material with the most robust in terms of pharmacokinetic and pharmacodynamic models inputs, and there is an adequate discussion of the differences in toxicokinetics between humans and animals.

RESPONSE 24: *No revisions were suggested.*

COMMENT 25: The effect and exposure biomarkers described are specific to the substances mentioned previously, although they are not actually for jet fuel, and this is very clear in the text. I have no major remarks on biomarkers issue.

RESPONSE 25: *No revisions were suggested.*

COMMENT 26: There is sufficient discussion of interactive effects with other substances and is focused on those effects that occur in hazardous waste sites. I think the "Profile" strives to discuss the mechanism of these interactions, but not appears a firm proposal on the actions to take; although I understand that this is part of ATSDR policy on this type of documents.

RESPONSE 26: *No revisions were suggested.*

COMMENT 27: About **POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE** I have nothing to comment.

RESPONSE 27: *No revisions were suggested.*

COMMENT 28: I feel that the "Profile" keeps a healthy distance from what is said in general to what could be a comprehensive clinical intervention, but it seems to me is the management of a severe acute case, more than those exposed chronically to jet fuels referred in the "Profile".

RESPONSE 28: *ATSDR did not identify information on methods for reducing chronic toxicity.*

COMMENT 29: I also feel that before considering whether there is a "well accepted" treatment, is whether the effects are reversible or irreversible, something that the "Profile" is imprecise or discussed very little, if anything, throughout the whole text.

RESPONSE 29: *ATSDR did not identify data that would allow for a determination of whether observed effects were reversible.*

COMMENT 30: A number of questions about the treatment deserve the involvement of a clinicians with sufficient experience in the medical care of these kind of patients, although it is intended to mention that the reference on the topic by the "Profile" be considered as only very general discussion regarding treatments that are known or expected to reduce peak absorption (lower initial blood levels) of the substance following exposure.

RESPONSE 31: *No revisions were suggested.*

COMMENT 32: I do not know other studies that can fill a data gap in this issue.

RESPONSE 32: *No revisions were suggested.*

COMMENT 33: I could understand that the Data Needs are presented in a neutral and non-judgmental fashion in order to avoid bias; however, I would be of the idea that the "Profile" is a document published by ATSDR, and this should be more critical and should adopt a position to strengthen the establishment of public health policies.

RESPONSE 33: *For chemicals of interest, ATSDR prepares Priority Data Needs documents, which contain more in-depth discussions of data gaps and needs and prioritize the needs for additional studies to be conducted.*

COMMENT 34: I think that paragraph 4 on page 25 practically repeats what described in Section 2.1 of Chapter 2; is it necessary appear again?

RESPONSE 34: *Because many users of the profile do not read the document from cover to cover, ATSDR believed that it was necessary to repeat this important background information before discussing the health effects.*

COMMENT 35: The studies listed on page 30, regarding the health effects by respiratory exposure to jet fuels not describe what statistical analysis test was performed and whether there was statistical or significance, nor described which covariables were under control.

RESPONSE 35: *It is beyond the scope of the profile to provide that level of detail for each study presented in Section 3.2. This section is intended to provide a synthesis and evaluation of the weight of evidence available for observed effects.*

COMMENT 36: Maybe it's a matter of style, but it would be worth to point out in separate subchapters by the results of studies conducted in humans and animals; these subsections would most notable the very limited information of the health effects on humans because exposure to jet fuels. I think it would be appropriate to make a final comment from the same "Profile" on the need to study a lot more about the health effects in human populations. I feel that much of what is said in the text is anecdotal or poorly protocolized.

RESPONSE 36: *ATSDR will consider the Reviewer's suggestion for subsections for human and animal data in subsequent revisions of the toxicological profile guidance. Currently, the profile is organized to*

discuss the human data prior to the animal data. ATSDR calls out the need for additional human studies in Section 3.12.2.

COMMENT 37: On page 36, in subchapter 3.2.1.3 Immunological and Lymphoreticular Effects, in the second paragraph are described things previously described on page 26. Is it absolutely necessary to repeat? Or, should decide in which part of the text would be better.

RESPONSE 37: *Since a number of the University of Arizona studies examined immunological effects, ATSDR included a very brief overview of the problems with these studies to provide background for interpreting the observed effects.*

COMMENT 38: On page 39, at the end where it says: "... The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are Recorded in Table 3-1 and plotted in Figure 3-1...." I think it should be mentioned results of the work of Limon-Flores AY, Chacón-Salinas R, Ramos G, Ullrich SE. Mast cells mediate the immune suppression induced by dermal exposure to JP-8 jet fuel Toxicol Sci 2009 Nov; 112 (1): 144-52], where it is proposed that the immunological effects by jet fuels are mediated by mast cells.

RESPONSE 38: *The Limon-Flores et al. (2009) study involved dermal exposure to JP-8 and is discussed in the dermal exposure section (Section 3.2.3.3).*

COMMENT 39: The Neurological Effects should be on top of all health effects being the most widely studied in both animals and humans, noted by the "Profile" itself.

RESPONSE 39: *For consistency across toxicological profiles, ATSDR presents the effects in the same order in every profile.*

COMMENT 40: I think the last paragraph on page 48 should be part of the respiratory effects of exposure by inhalation rather than orally because this appears by aspiration.

RESPONSE 41: *Since the primary route of exposure was oral, these studies are discussed in the oral exposure section.*

COMMENT 42: Regarding hematological effects generated by oral exposure, attract my attention because the disparity of the results in different animal species. Maybe make a comment about this be convenient.

RESPONSE 42: *As noted in several places in this section, the alterations observed in most studies were within the normal range and were not considered toxicologically significant.*

COMMENT 43: In relation with the above, and likewise, I do the marking on the frequent absence of studies on health effects in humans following oral exposure, especially in exposed workers or people who live in areas that are in proximity where use of this type of fuels is common.

RESPONSE 43: *No revisions were suggested.*

COMMENT 44: Description on page 78, about Physiologically Based Pharmacokinetic subchapter (PBPK) / pharmacodynamic (PD) Models, although the explanation is a very good one, it seems to me unnecessarily long. I think more or less the same circumstance in terms of TOXICITIES MEDIATED NEUROENDOCRINE THROUGH THE AXIS. On the basis that the “Profile” is not only for specialists looking for or know of toxicology issues of this kind of fuels, but also the general public, I think the explanation probably is unnecessary long.

RESPONSE 44: *ATSDR will consider the Reviewer’s suggestions in subsequent revisions of the toxicological profile guidance document.*

COMMENT 45: To the previous observation, must be add the issues regarding the CHILDREN’S SUSCEPTIBILITY, where the explanations are made with very well established arguments, also have the same defect of being very large; On the other hand, should be equally strong in arguments for susceptibility in elderly people and pregnant women with exposure to jet fuels, just to mention a few examples, as well as those adults who have chronic degenerative diseases such as diabetes mellitus type 2.

RESPONSE 45: *Discussion of adult populations which may be unusually susceptible to the toxicity of jet fuels is present in Section 3.10.*

COMMENT 46: One issue more, the BIOMARKERS OF EXPOSURE AND EFFECT (p. 87), I see that a very extensive explanation was also given.

RESPONSE 46: *ATSDR will consider the Reviewer’s suggestions in subsequent revisions of the toxicological profile guidance document.*

COMMENT 47: In relation to the first questions, I think there are not any data relevant to child health and developmental effects that have not been discussed in the profile and should be, and there are not any general issues relevant to child health that have not been discussed in the profile and should be

RESPONSE 47: *No revisions were suggested.*

COMMENT 48: I have no comments about Chapter 4 and 5. I’m not aware of any wrong or missing information.

RESPONSE 48: *No revisions were suggested.*

COMMENT 49 (Chapter 6): The document seems well aimed in monitoring to be given to the substances from the point of release to the environment until it reaches the receptor population and the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites.

RESPONSE 49: *No revisions were suggested.*

COMMENT 50 (Chapter 6): References to be included in this chapter are:

Proctor S, Heaton K, Smith K, Rodrigues E, McClean M. The occupational JP8 exposure neuroepidemiology study; evaluation of neuropsychological effects. *Occup Environ Med.* 2014 Jun;71 Suppl 1:A1-2.

Chao YC, Kupper LL, Serdar B, Egeghy PP, Rappaport SM, Nylander-French LA. Dermal exposure to jet fuel JP-8 significantly contributes to the production of urinary naphthols in fuel-cell maintenance workers. *Environ Health Perspect.* 2006 Feb; 114(2):182-5.

Mercant-Borna K, Rodrigues EG, Smith KW, Proctor SP, McClean MD. Characterization of Inhalation Exposure to Jet Fuel among U.S. Air Force Personnel *Ann Occup Hyg.*, Vol. 56, No. 6, pp. 736–745, 2012.

The conclusion of Proctor et al. (2014) is the reduced proficiency of tasks involving verbal memory and attention demonstrated among those with higher versus lower, current JP8 exposure. Significant associations were not observed between repeated-workday exposure to JP8 and neuropsychological performances. Results suggest that repeated JP-8 exposure, at levels not exceeding regulatory limits, does not significantly contribute to reduced neuropsychological proficiencies. Furthermore, Yi-Chun et al. (2006) conclude that the contribution of dermal exposure was significantly associated with levels of urinary 2-naphthol but not with urinary 1-naphthol among fuel-cell maintenance workers who wore supplied-air respirators. They conclude that dermal exposure to JP-8 significantly contributes to the systemic dose and affects the levels of urinary naphthalene metabolites. Finally, Mercant-Borna et al. (2012) point out that personal exposure to JP-8 varied by job and was positively associated with the relative humidity. However, self-reported exposure to JP-8 was an even stronger predictor of measured exposure than job title categories, suggesting that self-reported JP-8 exposure is a valid surrogate metric of exposure when personal air measurements are not available.

RESPONSE 50: *The Chao et al. (2006) study was added to Section 6.5; the Merchant-Borna et al. (2012) is already discussed in Section 6.5. Proctor et al. (2014) is an abstract and was not added to the profile. The health effects of the Merchant-Borna et al. (2012) study are discussed in Section 3.2; the Chao et al. (2006) findings on the relationship between dermal exposure and urinary 1- and 2-naphthol levels are discussed in Section 3.8.1.*

COMMENT 51: From my point of view, the "Profile" covers the relevant information concerning the transport, partitioning, transformation, and degradation of the substance in all media, as well as provides information on levels monitored or estimated in the environment, including background levels. The text describes adequately the 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. Despite this, it is noteworthy that the releases of JP-5, JP-8, and Jet A fuels to the air, soils and water are not required to be reported. I think is convenient to know and emphasize on the elements that support the idea that it is not necessary to report them

RESPONSE 51: *No revisions were suggested.*

COMMENT 52: Likewise, in subchapter 6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE (p. 157) does not indicate how were made the exposure categories (Workplaces?, Homogeneous exposure groups?, Kind of job?). Also, is not clear how the results were analyzed; I expected more complicated models, taking in account how or which other variables took part. This important and relevant information is not mentioned.

RESPONSE 52: *Section 6.5 was revised to identify the potential sources of jet fuel exposure in the general population and in occupationally exposed populations. The revised discussion of the occupational exposure populations includes information on job categories.*

COMMENT 53: Unfortunately, this chapter discusses largely what has been left undone, or information that should have. The chapter closes with a disappointing absence of "ongoing studies".

RESPONSE 53: *ATSDR did not identify any ongoing studies evaluating the potential for human exposure.*

COMMENT 54 (Chapter 7): In general the methods that have been included measured metabolites previously mentioned in the text. I'm not aware about additional methods that can be added to the tables, however, may be worth putting into perspective the usefulness of biomonitoring jet fuels in human biological samples and in environment samples by immunoassay test.

RESPONSE 54: *No revisions were suggested.*

COMMENT 55: In the "International" regulations, I should consider the List of MAK and BAT values 2013 del Deutsche Forschungsgemeinschaft, Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Report No. 49 which issues in his X chapter: Substances requiring special consideration: The Commission could not agree to assign a MAK ("maximale Arbeitsplatz-Konzentration": maximum workplace concentration) value to "gasolines" because this term describes a number of very different mixtures such as motor gasolines (petrol), special boiling point gasolines, white spirits and pyrolysis gasolines. The toxicity of gasolines depends primarily on their content of aromatic compounds (benzene, toluene, xylenes, ethyl benzene, cumene), which varies markedly with the production method. Procedures suggested for establishing MAK values by the mathematical evaluation of the composition of such mixtures of liquid solvents must be rejected on principle because such calculations cannot provide information as to the actual concentrations in the workplace air. Only when results are available from studies with defined gasoline-vapour mixtures can the Commission make any concrete statements. (BAT: "Biologische Arbeitsstoff-Toleranzwerte": biological tolerance values)

RESPONSE 55: *It is beyond the scope of the profile to include all international guideline and regulation values; thus, ATSDR limits the international values to the IARC cancer classification and WHO guideline values.*

COMMENT 56: In the **SUPPLEMENTAL DOCUMENT**, It is not understood very well how is structured the table (or matrix). As a reader, I see difficulties to make an overview or summary of what was found in the collected studies. I have to say that the studies do not contain the same subsections (Calculations, Comments, Results, etc.) There is no uniformity in the information. The "Calculations" in some cases are extremely large. I recommend if there is an interest in an article or any particular study, the reader must seek the original reference

RESPONSE 56: *The intent of the Supplemental Document is to provide additional information on the study design and results and to provide the reader with information on how ATSDR calculated exposure*

levels or doses. If there were no calculations or comments for a particular study, these headers were deleted. The format of the Supplemental Document follows the format of Section 3.2.

Review of Unpublished Studies

The Peer Reviewer reviewed the following unpublished studies and did not object to the inclusion of these studies in the profile.

Hurley JM, Wagner D, Sterner TR, et al. Acute Dermal Irritation Study of JP-8 and S-8 in New Zealand White Rabbits. [AFRL-RH-WP-TR-2011-0054].

Mattie DR, Cooper JR. Developmental Neurobehavioral Effects on JP-8 Jet Fuel on Pups from Female Sprague-Dawley Rats Exposed by Oral Gavage. [AFRL-HE-WP-TR-2001-0186].

Wagner MJ, Stevens SC, Guilfoil AJ, et al. Evaluation of Barrier Skin Cream Effectiveness Against JP-8 Jet Fuel Absorption and Irritation. [AFRL-RH-WP-TR-2009-0086].

Whitman FT, Hinz JP. Sensory Irritation Study in Mice: JP-5, JP-TS, JP-7, DFM, JP-10. [IOH-RS-BR-SR-2004-0001].

Mattie DR, Marit GB, Cooper JR, et al. Reproductive Effects of JP-8 Jet Fuel on Male and Female Sprague-Dawley Rats After Exposure by Oral Gavage. [AFRL-HE-WP-TR-2000-0067].

Comments provided by Peer Reviewer #3:

General Comments

COMMENT 1: This is an extremely comprehensive overview and review that brings together a lot of information from the testing of similarly named, but chemically diverse fuels, in diverse labs. As the document notes, the exact compositions of these fuels vary with their petroleum source, and will also vary with the refinery source (not mentioned in the text). The draft clearly indicates where the reported laboratory experimental measurements may have underestimated the actual exposure, i.e., aerosol inhalation vs. total (vapor + aerosol) inhalation.

RESPONSE 1: *The profile notes in several places (e.g., Sections 2.1, 3.2, and 4.1) that the composition of the jet fuel is dependent on the crude oil from which it is refined.*

COMMENT 2: I am not sure if it is mentioned in the individual publications, but the U of Arizona, Ullrich, Singh, McDougal, and Riviere studies were done using the same batch of JP-8. If it is, then that information should be included in the narrative. Definitive information on this issue may be available from the Air Force Office of Scientific Research. The studies were done under the watch of Dr. Walter Kozumbo, who has since retired.

RESPONSE 2: *Information on the fuel batch or source was not provided in all of the University of Arizona studies. If available, batch or source information was added to the supplemental document.*

COMMENT 3: To the best of my knowledge, there are Air Force, and other military, regulations for personal protective gear for people doing aircraft maintenance, particularly for those working in or around the fuel tanks, and the fuel tank contents. Unfortunately, I do not have access to any of these.

RESPONSE 3: *ATSDR has requested this information from DoD; DoD-provided information will be incorporated into the post-public comment profile.*

COMMENT 4: There are a number of references, including a recent book, *Jet Fuel Toxicology*, that are not included in the report, but should be. They are appended to this review.

RESPONSE 4: *The Reviewer provided copies of the Chao et al. (2006), Limón-Flores et al. (2009), and Merchant-Borna et al. (2012) studies; these studies are cited in the profile. The Proctor et al. (2014) study is only available as an abstract and was not added to the profile.*

COMMENT 5: What are the designations + and * in the References?

RESPONSE 5: *As noted on the first page of Chapter 9, * indicates cited in text and + indicates cited in Supplemental Document.*

COMMENT 6: In the introductory, and other, sections, there is much mention of skin irritation, and effects in animals only in the presence of this irritation. However, skin irritation is a relative term which can be used for a slight rash or for drying and cracking, with bleeding and necrosis. Most of the dermal effects seen in animals following prolonged exposure, or high doses, were severe, and beyond the realm

of what many would consider “irritation.” The lower volatility of these fuels, compared for example, to gasoline, is the reason for this irritation. In fact, the severe reactions are the primary reason for avoiding skin contact.

RESPONSE 6: *The text in Chapters 1 and 2 was revised to provide a better description of the dermal effects rather than referring to using the generic term of “irritation”. The text in Sections 2.2 and 3.2.3.2 also includes a comparison of the results of an animal study in which the jet fuel was applied under occluded and non-occluded condition; this indirectly addresses the issue of volatility.*

COMMENT 7: There are a number of references to “deodorized kerosene” being tested, as opposed to kerosene. I was not able to find an explanation of how this differs from kerosene, or whether it is just a difference in nomenclature.

RESPONSE 7: *Deodorized kerosene is a treated kerosene product.*

COMMENT 8: Is there any information regarding the exposure levels to the people who would most likely be exposed, e.g., aircraft maintenance workers, fuel workers, flight line, etc.? i.e., how do the experimental rodent exposure levels relate to the human exposure?

RESPONSE 8: *A discussion of occupational exposure levels is included in Section 6.5. Many of these studies examined jet fuel components; thus, they cannot be directly compared to exposure levels in laboratory animal studies.*

COMMENT 9: Personnel exposure levels are mentioned in sect. 3.2.1.4 (neurological effects). It would be helpful if these exposure levels were included in the preceding narratives of rodent studies in order to directly relate the rodent exposures to actual, human exposures.

RESPONSE 9: *See Response to Comment 10.*

COMMENT 10: Sect. 3.2.1.3. Immunological effects, Dermal effects [pg. 73]. There is no mention of the reaction of individuals who get JP-8 or Jet-A on their skin (not as controlled studies, but during work exposure), e.g., severe erythema, drying, ulceration, etc.

RESPONSE 10: *ATSDR did not identify any studies reporting immunological effects in humans following dermal exposure. The effects listed by the Reviewer (e.g., severe erythema, drying, ulceration) would be discussed under dermal effects; as with immunological effects, ATSDR did not identify studies examining dermal effects following dermal exposure.*

COMMENT 11: Sect. 3.3. Genotoxicity; pg. 70. 1. 27-29 [Krieg ref.]. What cells were sampled for the comet assay?

RESPONSE 11: *The text was revised to indicate that the comet assay was conducted in leukocytes.*

COMMENT 12: With regard to the statement in various places in this document that there are no studies in humans of the carcinogenicity of these fuels – is may be worth mentioning that there are studies in

humans of benzene which is a component of the fuels, and the results of those studies; i.e., it is a human carcinogen. Also, a number of additional components of the fuels, including naphthalene, have been classified as probable or possible human carcinogens.

RESPONSE 12: *Although there are adequate data to evaluate the carcinogenicity (as well as other health effects) of some of the individual components of jet fuels, ATSDR chose to only discuss the health effects of the mixture. A statement was added to Section 3.1 indicating that the focus of the profile was exposure to JP-5, JP-8, and Jet A fuel mixture and refers the reader to toxicological profiles on some of the individual components.*

COMMENT 13: A number of additional, relevant references are included with this review.

The following book, published in 2011, Primarily addresses JP-8.

Witten ML, Zeiger E, Ritchie GD. 2011. *Jet Fuel Toxicology*. CRC Press/Taylor and Francis, 324 pp. [ISBN: 978-1-4200-8020-9]

Although much of the information in this book is already in the ATSDR draft, some of the chapters contain relevant research publications not addressed in the draft. The following is an incomplete list.

Cavallo et al., *Toxicology* 223(1-2):26-35, 2006. (genotoxic effects in exposed airport personnel)

McDougal and Rogers, *Toxicol Lett* 149(1-3):301-308, 2004. (human dermal exposure)

McDougal et al., *Toxicol Sci* 95(2):495-510, 2007. (rat dermal effects)

Ramos et al., *Toxicol Sci* 108(1):100-109, 2009. (immunological)

RESPONSE 13: *The McDougal et al. (2007) and Ramos et al. (2009) studies were added to the profile. The Cavallo et al. (2006) paper was not added because it involved mixed exposure to Jet A, Jet A exhaust, and gasoline/diesel exhaust. McDougal and Rogers (2004) review was evaluated to identify uncited studies.*

COMMENT 14: The following are additional articles I am aware of that are not referenced in the Draft, but should be addressed. It was not clear from the abstracts that I got off ToxLine if all of these articles addressed JP-5 or JP-8. The proteomic studies papers, although they do not relate directly to clinical effects, are biomarkers of the fuel in those tissues. They also are a measure of dose-related organ effects and suggest possible clinical sequelae.

Kaufman LR, et al. Effects of concurrent noise and jet fuel exposure on hearing loss. *J Occup Environ Med.* 47(3):212-218, 2005.

We sought to examine the effects of occupational exposure to jet fuel on hearing in military workers. METHODS: Noise-exposed subjects, with or without jet fuel exposure, underwent hearing tests. Work histories, recreational exposures, protective equipment, medical histories, alcohol, smoking, and demographics were collected by questionnaire. Jet fuel, solvent, and noise exposure data were collected from records. Fuel exposure estimates were less than 34% of the OSHA Threshold Limit Values.

RESULTS: Subjects with 3 years of jet fuel exposure had a 70% increase in adjusted odds of hearing loss (OR=1.7; 95% CI=1.14–2.53) and the odds increased to 2.41 (95% CI=1.04–5.57) for 12 years of noise and fuel exposure.

CONCLUSIONS: These findings suggest that jet fuel has a toxic affect on the auditory system.

Reutman SR, et al. Evidence of reproductive endocrine effects in women with occupational fuel and solvent exposures. *Environ Health Perspect.* 110(8):805-811, 2002.

Hydrocarbons (HCs) found in fuels and solvents are ubiquitous in the environment, yet we know little about their effects on the endocrine system. The objective of this study was to assess the potential reproductive endocrine effects of low-dose HCs encountered by female U.S. Air Force personnel with fuel (primarily JP-8 jet fuel) and solvent exposures (n=63). We estimated the internal dose of HCs in fuels and solvents by measuring their levels in exhaled breath, including the sum of aliphatic HCs (C₆H₁₄-C₁₆H₃₄) and the sum of aromatic HCs (benzene, ethylbenzene, toluene, and m,p,o-xylenes). Adverse outcome measures included urinary endocrine markers that have been associated with nonconceptive (vs. conceptive) menstrual cycles in ovulatory women: lower preovulatory luteinizing hormone (LH) and mid-luteal phase pregnanediol 3-glucuronide (Pd3G) and estrone 3-glucuronide, and higher follicle phase Pd3G. We also obtained reproductive and exposure information from baseline questionnaires and daily diaries. Toluene was the most frequently found analyte in the breath, with values up to 52.0 ppb, and benzene breath levels were up to 97.5 ppb. Regression analysis revealed that preovulatory LH levels were significantly lower (p=0.007) among women whose total aliphatic HC levels were above the median. The relationship between elevated aliphatic HC exposure and lowered preovulatory LH levels in the present study suggests that compounds in fuels and some solvents may act as reproductive endocrine disruptors. Confirmation of these findings is needed, not only to determine if fuel and solvent exposure may impact other LH-dependent physiologic functions but also to examine effects of fuels and solvents on conception.

Lemasters GK, et al. Male reproductive effects of solvent and fuel exposure during aircraft maintenance. *Reprod Toxicol.* 13(3):155-166, 1999.

Few studies have addressed the effects of mixed, low-level exposures to complex mixtures on a man's reproductive potential. In this prospective study, each subject was evaluated before first exposure and at 15 and 30 weeks after exposures had begun. A total of 50 men working on aircraft maintenance at an Air Force installation were included in the study. In addition, eight unexposed men were concurrently sampled. Industrial hygiene (IH) sampling and expired breath samples were collected for jet fuel as measured by total naphthas, benzene--a component of jet fuel, 1,1,1-trichloroethane, methyl ethyl ketone, xylenes, toluene, and methylene chloride. Sperm production, structure, and function (sperm concentration, sperm motion, viability, morphology, morphometrics, and stability of sperm chromatin) were evaluated. Exposures were low. All mean IH measures were below 6 ppm, which is less than 10% of the Occupational Safety and Health Administration standard for all chemicals except benzene. Sheet metal workers had the highest mean breath levels for both total solvents (24 ppb) and fuels (28.3 ppb). For most sperm measures, mean values remained in the normal range throughout the 30 weeks of exposure. When jobs were analyzed by exposure groups, some adverse changes were observed. The paint shop group had a significant decline in motility of 19.5% at 30 weeks. Internal dose measures, however, did not show a significant association with spermatogenic changes.

Lemasters GK, et al. Comparison of internal dose measures of solvents in breath, blood and urine and genotoxic changes in aircraft maintenance personnel. *Drug Chem Toxicol.* 22(1):181-200, 1999.

Solvents and fuels are in widespread use both in civilian and military populations.

1,1,1-trichloroethane (TCA), xylene, toluene, methyl ethyl ketone (MEK) and methylene chloride are found in a variety of compounds including degreasing agents, paints, coatings, pesticides and paint strippers. Toluene and xylene are also found in fuels, which are complex mixtures of hundreds of

agents. The purpose of this investigation was twofold. The first was to determine the optimum medium to measure internal dose of solvents comparing blood, urine and breath. The second was to determine if low level exposures were associated with genotoxic changes after a short-term exposure of fifteen or thirty weeks. To accomplish the first goal a pilot study was initiated involving eight volunteers who worked in aircraft maintenance including sheet metal, painting and assembly mechanic jobs. Industrial hygiene measurements were evaluated over 30 working days. Breath, blood and a 24-hour urine sample were collected twice to compare internal dose parameters. To achieve the second goal, 58 newly hired subjects were monitored prior to exposure and over 30 weeks to determine if there were genotoxic changes as a result of solvent and/or fuel exposure as measured by sister chromatid exchanges (SCEs) and micronuclei (MN). Exposure groups included workers involved in sheet metal (fuel cell) activities, painting, fueling operations and flight line. Results of the pilot study demonstrated that industrial hygiene air samples and internal breath measures taken on the same day were highly correlated for measuring TCA ($r=0.93$) and toluene ($r=0.90$) but was not as well correlated for the other compounds. Breath measures were more sensitive for measuring low level exposure than were either analytes in blood or 24-hour urine samples; these latter two measures were usually below the limit of detection. A small but statistically significant increase in the frequency of SCEs occurred after 30 weeks of exposure for sheet metal workers ($p=0.003$) and for painters ($p=0.05$). The MN frequency in the sheet metal workers initially showed a significant increase by 15 weeks, but by 30 weeks had decreased. Chance occurrence of exposures to other occupational or non-occupational agents can not be eliminated as a cause of the genotoxic results since between 58 and 93 total analytes could be found in the breath of some aircraft maintenance personnel.

Witzmann FA, et al. Proteomic analysis of simulated occupational jet fuel exposure in the lung. *Electrophoresis* 20(18):3659-3669, 1999.

We analyzed protein expression in the cytosolic fraction prepared from whole lung tissue in male Swiss-Webster mice exposed 1 h/day for seven days to aerosolized JP-8 jet fuel at concentrations of 1000 and 2500 mg/m³, simulating military occupational exposure. Lung cytosol samples were solubilized and separated via large scale, high resolution two-dimensional electrophoresis (2-DE) and gel patterns scanned, digitized and processed for statistical analysis. Significant quantitative and qualitative changes in tissue cytosol proteins resulted from jet fuel exposure. Several of the altered proteins were identified by peptide mass fingerprinting, confirmed by sequence tag analysis, and related to impaired protein synthetic machinery, toxic/metabolic stress and detoxification systems, ultrastructural damage, and functional responses to CO₂ handling, acid-base homeostasis and fluid secretion. These results demonstrate a significant but comparatively moderate JP-8 effect on protein expression and corroborate previous morphological and biochemical evidence. Further molecular marker development and mechanistic inferences from these observations await proteomic analysis of whole tissue homogenates and other cell compartment, i.e., mitochondria, microsomes, and nuclei of lung and other targets.

Witzmann FA, et al. *Electrophoresis* 21(5):976-984, 2000. Proteomic analysis of the renal effects of simulated occupational jet fuel exposure.

We analyzed protein expression in the cytosolic fraction prepared from whole kidneys in male Swiss-Webster mice exposed 1 h/day for five days to aerosolized JP-8 jet fuel at a concentration of 1000 mg/m³, simulating military occupational exposure. Kidney cytosol samples were solubilized and separated via large-scale, high-resolution two-dimensional electrophoresis (2-DE) and gel patterns scanned, digitized and processed for statistical analysis. Significant changes in soluble kidney proteins resulted from jet fuel exposure. Several of the altered proteins were identified by peptide mass finger-printing and related to ultrastructural abnormalities, altered protein processing, metabolic effects, and paradoxical stress protein/detoxification system responses. These results demonstrate a significant but comparatively moderate JP-8 effect on protein expression in the kidney

and provide novel molecular evidence of JP-8 nephrotoxicity. Human risk is suggested by these data but conclusive assessment awaits a noninvasive search for biomarkers in JP-8 exposed humans.

Witzmann FA, et al. Analysis of rat testicular protein expression following 91-day exposure to JP-8 jet fuel vapor. *Proteomics* 3(6):1016-1027, 2003.

We analyzed protein expression in preparations from whole testis in adult male Sprague-Dawley rats exposed for 6 h/d for 91 consecutive days to jet propulsion fuel-8 (JP-8) in the vapor phase (0, 250, 500, or 1000 mg/m³ +/- 10%), simulating a range of possible human occupational exposures. Whole body inhalation exposures were carefully controlled to eliminate aerosol phase, and subjects were sacrificed within 48 h postexposure. Organ fractions were solubilized and separated via large-scale, high resolution two-dimensional electrophoresis, and gel patterns scanned, digitized and processed for statistical analysis. Seventy-six different testis proteins were significantly increased or decreased in abundance in vapor-exposed groups, compared to controls, and dose-response profiles were often nonlinear. A number of the proteins were identified by peptide mass fingerprinting and related to histopathological or physiological deficits shown in previously published studies to occur with repeated exposure to hydrocarbon fuels or solvents. These results demonstrate a significant effect of JP-8 exposure on protein expression, particularly in protein expression in the rodent testis, and suggest that a 91 d exposure to jet fuel vapor induces changes of equal or greater magnitude to those reported previously for shorter duration JP-8 aerosol exposures.

Drake MG, et al. JP-8 jet fuel exposure alters protein expression in the lung. *Toxicology* 191(2-3):199-210, 2003.

The purpose of this study was to investigate the proteomic mechanisms of Jet Propulsion-8 (JP-8) toxicity in the lung, specifically relating to lung epithelial cell apoptosis and edema. Male Swiss-Webster mice were exposed to 1h/day aerosolized JP-8 jet fuel at concentrations of 250, 1000, and 2500 mg/m³ for 7 days. Lung cytosol and whole lung samples were solubilized, separated via large scale, high-resolution two-dimensional electrophoresis, and processed for analysis. Significant quantitative differences in lung protein expression were found as a result of JP-8 exposure. At 250 mg/m³ JP-8 concentration, 31 proteins exhibited increased expression, while 10 showed decreased expression. At 1000 mg/m³ exposure levels, 21 lung proteins exhibited increased expression and 99 demonstrated decreased expression. At 2500 mg/m³, 30 exhibited increased expression, while 135 showed decreased expression. Several of the proteins were identified by peptide mass fingerprinting, and were found to relate to cell structure, cell proliferation, protein repair, and apoptosis. These data demonstrate the significant stress JP-8 jet fuel puts on lung epithelium. Furthermore, there was a decrease in alpha1-anti-trypsin expression suggesting that JP-8 jet fuel exposure may have implications for the development of pulmonary disorders.

RESPONSE 14: ATSDR has reviewed the Reviewer's suggested literature and added the Witzmann et al. (1999) and Drake et al. (2003) proteomics studies to the profile. The Reutman et al. (2002) paper is the same study as Army (2001); the published paper citation was added to the profile. The Witzmann et al. (2000, 2003) proteomics studies were not added to the profile because the toxicological significances of the alterations in protein levels in the kidneys or testes of mice are not known since histological alterations have not been found in the kidneys or testes of mice exposed via inhalation to JP-8. The Kaufman et al. (2005) paper was not included in the profile because the workers were predominantly exposed to JP-4. The two Lemasters et al. (1999) studies examined workers exposed to a variety of solvents; the second Lemasters et al. (1999) study (*Reprod Toxicol* 13(3):155-166) also examined fuel maintenance workers who were exposed to JP-4.

Annotations and Comments on the Toxicological Profile

COMMENT 1 (page 1, line 25): JP-8 is also used as a general military fuel for ground vehicles and heating oil in lieu of diesel and kerosene in the field so that they do not have to transport and maintain separate fuel types.

RESPONSE 1: *The text was revised to include the use of JP-8 as a fuel source for land vehicles, heaters, and lights.*

COMMENT 2 (page 1, lines 26-27): JP-8 is Jet A plus additives.

RESPONSE 2: *Although JP-8 is essentially Jet A with additives, this statement is referring to the use of Jet A fuel by the military.*

COMMENT 3 (page 1, lines 28-29): The reviewer made the following suggested revision to the sentence: The *different fuels are made of a number of* ~~are made of a number of~~ *comprise more than 1000 of the same chemicals, but in different proportions.*

RESPONSE 3: *The intention of the referenced sentence was to indicate that jet fuels are comprised of a large number of chemicals; the Reviewer's suggestions change the meaning of the statement to a comparison of the different fuels. ATSDR does not agree with the suggested revision since the fuels are defined by their performance specifications (e.g., physical properties) rather than their chemical composition.*

COMMENT 4 (page 2, line 4): The number and types of chemicals should be put into perspective with respect to gasoline to which all segments of the public are routinely exposed. The Reviewer suggested the following statement be added to the end of the sentence: *many of which are also present in gasoline.*

RESPONSE 4: *The suggested revision was made.*

COMMENT 5 (page 2, line 35): There also can be high exposure for airline mechanics and maintenance workers. Also, people on the tarmac or flight line are exposed to air-borne aerosols of unburned fuel during engine startup procedures.

RESPONSE 5: *A statement was added regarding the potential for exposure for workers involved in aircraft or fuel tank maintenance or for individuals in the vicinity of the aircraft during a cold engine startup.*

COMMENT 6 (page 3, line 19): The Reviewer suggested the following revision: The chemicals in JP-5, JP-8, or Jet A fuels will be eliminated from the body in the urine, feces, *or breath.*

RESPONSE 6: *The suggested revision was made.*

COMMENT 7 (page 5, lines 30-31): The Reviewer suggested the following revision: However, the detection of these chemicals or their metabolites may also come from several sources other than the jet

fuels, including exposure to gasoline fumes when filling the car's tank, and cannot predict the kind of health effects that might develop from that exposure.

RESPONSE 7: *The suggested revision was made.*

COMMENT 8 (page 6, lines 12-13): The Reviewer suggested the following sentence be added: *The military also has developed guidelines for military personnel working with fuels, or on aircraft or on the flight line.* The Reviewer also noted "I know that these guidelines or regulations exist, but do not have access to them or to their cites."

RESPONSE 8: *ATSDR has requested this information from DoD; the information will be added to the post-public comment profile.*

COMMENT 9 (page 8, lines 18-19): The Reviewer suggested the following revision: Many of the constituents of JP-5, JP-8, and Jet A fuels are volatile and will evaporate into the air when jet fuels are spilled accidentally onto soils or surface waters; *others tend to be "oily" and do not evaporate easily, if at all.*

RESPONSE 9: *The referenced sentence is only referring to the volatile components; other components are discussed in subsequent sentences.*

COMMENT 10 (page 9, line 18): higher odds or higher frequencies?

RESPONSE 10: *The study found significantly higher odds ratios.*

COMMENT 11 (page 9, line 18): The Reviewer suggested moving the sentence--*Limited information is available on the carcinogenic potential of jet fuels*—to line 24.

RESPONSE 11: *The suggested revision was not made to be consistent with the rest of the paragraph in which the human data are discussed before the animal data. The sentence in question was revised to clarify that there are limited data available on the carcinogenicity of jet fuels in humans.*

COMMENT 12 (page 10, lines 22 and 24): The Reviewer suggested two editorial revisions: change tract to *tracts* and add *days* after 90.

RESPONSE 12: *The suggested revisions were made.*

COMMENT 13 (page 11, line 17): The descriptions of these studies should mention whether the skin was occluded or left open after fuel administration. It makes a difference in the severity of the response.

RESPONSE 13: *The suggested revision was made.*

COMMENT 14: The Reviewer suggested the following revision: The principal source of JP-8-induced irritation in pigs was reported to be *the larger molecule* aliphatic hydrocarbons such as tridecane, tetradecane, and pentadecane (Muhamamad et al. 2005b).

RESPONSE 14: *The study only examined larger hydrocarbons; ATSDR believes that the suggested revision maybe misleading.*

COMMENT 15 (page 13, line 31): The Reviewer suggested the following revision: In laboratory animals, JP-5 and JP-8 caused alterations in performance in *a battery of* tests in rats exposed to 1,200 mg/m³ JP-5 vapor or 1,000 mg/m³ JP-8 vapor in intermediate-duration inhalation studies

RESPONSE 15: *The suggested revision was made.*

COMMENT 16 (page 14, line 16): The Reviewer suggested the following revision: Inhalation (University of Arizona study, which only measured the aerosol component) or oral (1,000 mg/kg/day) exposure of pregnant mice to JP-8 resulted in suppressed immune function in the offspring *when* assessed before 8 weeks of age (Harris et al. 2007b; Keil et al. 2003).

RESPONSE 16: *The suggested revision was made.*

COMMENT 17 (page 14, line 25): The Reviewer noted that carcinogenicity is explained later in this paragraph and suggested the following revisions: An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (~~noncarcinogenic~~) over a specified duration of exposure.

RESPONSE 17: *To emphasize that the MRLs are based on noncarcinogenic effects, the suggested revision was not made.*

COMMENT 18 (page 15, lines 21, 25, 27, and 31): The Reviewer suggested changing vapor plus aerosol to *vapor plus aerosol*.

RESPONSE 18: *The suggested revision was not made; ATSDR believes that it is more accurate to describe the test atmosphere as containing vapor and aerosol components.*

COMMENT 19 (page 25, line 29): Do you mean end points, or ‘effects’? Effects is a more appropriate word.

RESPONSE 19: *End points was changed to effects.*

COMMENT 20 (page 72, Table 3-4): Need to add exposure route.

RESPONSE 20: *The suggested revision was made.*

COMMENT 21 (page 72, Table 3-4): Misleading header; delete. This term is typically used for *in vitro* cell culture studies. A better heading would be “Mammalian – *in vivo*.”

RESPONSE 21: *The header row was deleted.*

COMMENT 22 (page 73, lines 20-21): This is a misleading statement. There certainly are data on the metabolism and distribution of benzene, naphthalene, toluene, etc.

RESPONSE 22: *The text was revised to indicate that there were no data on the metabolism of JP-5, JP-8, or Jet A fuels. Additionally, a statement was added that data are available for individual components and refers the reader to toxicological profiles for benzene, toluene, xylenes, ethylbenzene, and naphthalene.*

COMMENT 23 (page 75, lines 7-10): Incomplete sentence.

RESPONSE 23: *The referenced sentence was deleted.*

COMMENT 24 (page 76, line 32): The Reviewer suggested changing “on” to “of”.

RESPONSE 24: *The suggested revision was made.*

COMMENT 25 (page 78, lines 8-9): There are metabolic pathway data on some of the components (see COMMENT #22).

RESPONSE 25: *The referenced sentence was revised to indicate that there were no data on the metabolic pathway of JP-5, JP-8, or Jet A fuel. A statement was added to Section 3.4 that toxicokinetic data are available for individual components of jet fuels and refers the reader to ATSDR toxicological profiles on benzene, toluene, xylenes, ethylbenzene, and naphthalene.*

COMMENT 26 (page 89, line 2): It may be better to say “time spent working in the fuel tank”

RESPONSE 26: *The sentence was revised to indicate that time spent in the fuel tank was a significant predictor of 1- and 2-naphthol levels.*

COMMENT 27 (page 99, line 32): It is not clear what is meant by a “lower” association.

RESPONSE 27: *The word “lower” was deleted.*

COMMENT 28 (page 101, line 11): The Reviewer suggested changing “foreign” to “other”.

RESPONSE 28: *The suggested revision was made.*

COMMENT 29 (page 112, Table 4-3): There should be a footnote to point out to the reader that the substances in this list account for only 41% of the total composition.

RESPONSE 29: *A footnote was added that the analysis did not include all JP-5 components.*

COMMENT 30 (page 113, Table 4-4): See comment for Table 4-3.

RESPONSE 30: *A footnote was added that the analysis did not include all JP-8 components*

COMMENT 31 (Table 115, Table 4-5): Is it really necessary to add a reference (d) to the fact that these fuels are liquids?

RESPONSE 31: *It is standard to include the physical state in this profile table.*

COMMENT 32 (page 141, line 20): They are also released as aerosols during engine start-up procedures.

RESPONSE 32: *The Reviewer did not provide a citation for this statement.*

COMMENT 33 (page 142, line 1): Because JP-8 is used as a diesel fuel in military vehicles during ground operations and for field cookstoves, those personnel can also be exposed.

RESPONSE 33: *A statement was added that exposure can also occur from the use of JP-8 as a fuel source for military vehicles or for heating or lighting sources.*

COMMENT 34 (page 159, line 21): The Reviewer suggested the following revision: Children residing on or near military bases where JP-8 and JP-5 are used may experience a slightly higher level of exposure than children of the general population.

RESPONSE 34: *The suggested revision was made.*

COMMENT 35 (page 202, line 22): The Reviewer corrected the authors on the Mattie et al. 2000 paper.

RESPONSE 35: *The suggested revision was made.*

Review of Unpublished Studies

The Peer Reviewer reviewed the following unpublished studies and did not object to the inclusion of these studies in the profile.

Hurley JM, Wagner D, Sterner TR, et al. 2011. Acute Dermal Irritation Study of JP-8 and S-8 in New Zealand White Rabbits. [AFRL-RH-WP-TR-2011-0054].

Mattie DR, Cooper JR. 2001. Developmental Neurobehavioral Effects on JP-8 Jet Fuel on Pups from Female Sprague-Dawley Rats Exposed by Oral Gavage. [AFRL-HE-WP-TR-2001-0186].

Wagner MJ, Stevens SC, Guilfoil AJ, et al. 2009. Evaluation of Barrier Skin Cream Effectiveness Against JP-8 Jet Fuel Absorption and Irritation. [AFRL-RH-WP-TR-2009-0086].

Whitman FT, Hinz JP. 2004. Sensory Irritation Study in Mice: JP-5, JP-TS, JP-7, DFM, JP-10. [IOH-RS-BR-SR-2004-0001].

Mattie DR, Marit GB, Cooper JR, et al. 2000. Reproductive Effects of JP-8 Jet Fuel on Male and Female Sprague-Dawley Rats After Exposure by Oral Gavage. [AFRL-HE-WP-TR-2000-0067].