NASA REVIEW/COMMENTS ON DRAFT EPA TCE IRIS RISK ASSESSMENT

Submitted August, 26, 2009

NASA thanks EPA for the opportunity to review and comment on the draft IRIS risk assessment for Trichloroethylene (TCE). We are providing a summary of our issues and comments.

EPA, NASA, DoD, and DOE collaborated in the initial stage of this assessment process by requesting impartial and informed direction from the National Academy of Sciences (NAS) on TCE exposure. That collaborative effort was executed as a first step with the option to return to NAS for formal peer review of the draft assessment. NASA welcomes the opportunity to continue this collaborative effort to promote sound science policy development. We suggest addressing outstanding technical and scientific issues identified through the proposed second phase, NAS peer review of the draft TCE IRIS document. Use of the NAS for peer review for such a complex, large risk assessment supports continuing use of sound science in decision making and EPA's authority over the development of the draft and final IRIS risk assessment for TCE

The draft TCE risk assessment is a very large (in excess of 1400 pages, including Appendices) and complex review of the current literature and EPA's approach to develop values for use in remediation of TCE contaminated media. The size and complexity of the TCE draft necessitates that NASA summarize the outstanding scientific issues, supported by specific examples from the draft text rather than provide line by line review. NASA provides comments and suggested recommendations to strengthen EPA's draft and support public review of this complex draft assessment. NASA's comments center on scientific and technical issues and do not address typographical errors or format issues.

In our comments, NASA will discuss the larger issues of concern and identify specific targeted concerns, highlighting draft text and provide input and recommendations, where appropriate. NASA encourages EPA to evaluate and address the weaknesses, uncertainty and specific limitations of the use of the body of literature, models for the estimation of dose-response relationships, identification of the Mode of Action, assessment of the carcinogenicity risk, and the setting of RfD, RfC and cancer values. If possible, we suggest EPA address the interagency input prior to the peer review. If that option is not possible, NASA requests that the peer review charge questions should address the identified outstanding issues and request targeted review and comment by the NAS peer review team.

Upon review of the draft, NASA identified several key issues of concern, targeting the appearance of EPA not following established EPA policies or proven methodologies, provision of a literature search but no critical evaluation across the various studies or supporting meta-analysis, and differing conclusions from previous NAS, IOM and internal EPA scientist publications.

<u>MODELING/METHODOLOGY:</u> Upon review, NASA identified specific analyses that require additional clarification, substantiation or explanation:

- Section 3.5.4.2, Page 135: EPA's decision to not include oxidative metabolism of TCE by the kidney is contrary to data that humans, rats and mice exhibit kidney metabolism that that could significantly clear TCE from the kidney, based on blood flow (Lipscomb JC, et al, Risk Anal.2003: 23 (6) 1221-38)

- Section 3.5.5.1. Page 141: EPA needs to clarify its assumption to pool kinetic data across genders and strains as gender differences may identify significant information on metabolic processes. EPA also utilized limited mice data and did not consider studies by Kim et al, Toxicol. Appl. Pharmacol (2009), Sweeney LM et al, Toxicology, (2009); 260, 77-83.

- Table 3.5.4, Page 143: EPA did not use applicable studies on rats, such as Birner et al, Arch Toxicol. (1997), raising questions on the consistency and applicability of the existing model used in this draft assessment.

- Table 3.5.8, Page 158 and Table 3.5.9, Page 158: EPA developed posterior distributions of partition coefficients for TCE and metabolites in rats demonstrating wide ranges (representing for 95% of the population with 10-fold differences). Such wide ranges for these partition coefficients is very unlikely and is contrary to documented studies' findings that reject such extensive variability for partition coefficients. EPA also provided very large and unsubstantiated estimates for humans, rats and mice without supporting animal data, suggesting the need to recalibrate the mouse model applied to TCE and its metabolites.

- Section 3.5.6.3, Page 161: EPA provides limited explanation or supporting documentation to evaluate the relationship between the data, assumptions, models (goodness of fit).

- Section 3.5.6.4, Page 174: In addition, EPA does not provide sensitivity analyses of the TCE PBPK model utilized in this draft assessment. This is in direct conflict with existing EPA policy that states, " it is important to carry out sensitivity analysis under conditions reflecting the studies providing the data for model calibration (i.e. pharmacokinetic studies) under conditions appropriate for estimate dose metrics in critical studies and finally under conditions appropriate for the risk"(US EPA, Approaches for the Allocation of Physiologically Based Pharmacokinetic PBPK) Models and Supporting Data in Risk Assessment, National Center for Environmental Assessment, Washington DC; EPA/600/R-05/043F, (2006)). This is especially important to clarify EPA's use of dose estimates, areas of uncertainty, and interspecies variability (mice, rats, and humans) due to the direct relevance to EPA's calculation of RfDs, RfCs and chosen cancer risk level.

- Figures 3.5.5. and 3.5.6, Pages 178-179: EPA's relies on the GSH Conjugation Pathway for rodents and the related derivation of cRfCs and cRfDs target kidney effects as a key noncancer effect. However, EPA's use of the GSH pathway, as defined, generate median populations with significant levels of uncertainty that impact on the development of estimated RfDs and RfC levels (to levels of 300-400 fold). Update of this model to address these significant uncertainties

and the established EPA requirement for sensitivity analysis are needed to permit interspecies extrapolation.

- Section 3.5.7.2.2, Page 191: EPA states that the predictions from the GSH conjugation for mice and rats, "remain more uncertain" than the human predictions, underscoring NASA concern over EPA's reliance on the GSH pathway. Based on the demonstrated weaknesses of the rat and mice data, EPA should not use these data in this risk assessment.

- Sections 5.1, Page 1030, 5.1.3.1, Page 1063, and 5.1.3.1, Page 1077: EPA should discuss and clarify its assumptions to address limitations and uncertainties related to application of the PBPK model within a species, including assessment across genders, age, and strain of animal in estimating internal dose. As written, the reader is left with the understanding that EPA is not assuming any potential differences. In particular, EPA needs to clarify its assumptions related to dose metrics for the GSH pathway in rodents to ensure the PBPK model reflects current understanding of this specific pathway.

- Section 5.1.3.2, Page 1073: EPA's use of the 99^{th} percentile, not the generally accepted 95^{th} percentile, for the population distribution of the "sensitive" individual is unsupported and requires explanation for this alternative choice.

- Section 6.1.3: In Section 5, EPA applied a screening process for non-cancer dose-response assessment with specific directions that are counter to current, established approaches, including direction to, "reduce the number of endpoints and studies those that would best inform the selection of critical effects" and identify the more sensitive end points" and considered "all studies described in Chapter 4 which report adverse non-cancer heal effects and provide quantitative dose-response data (page 1029). EPA noted that this approach was "in contrast to the approach used in most assessments". Use of this alternative approach is not justified or credible, as it provides no consideration of data quality, potential for bias, weight of evidence, positive or negative results and discounts all but the most conservative results. EPA does not substantiate the need or applicability of such a radical departure from proven, accepted risk assessment approaches. EPA's assertion that this alternative approach "provides robust estimates of the RfC and RfD" (page 1030) lacks substantiation and again is counter to established risk assessment approaches. This clarification and defense of this alternative approach should be provided in Section 5 and in Section 6.1.3

- Section 6.1.4: EPA provided a detailed assessment of specific aspects of uncertainty. To ensure completeness, EPA needs to submit additional discussion on the following issues; limitations with rodent kidney dosimetry, limitations in identified animal cancer studies, and evaluation challenges when determining the significance of rare tumors. This clarifying language should also be included in Section 5 to provide justification of applied uncertainty.

- Appendix A, Pages A-69- A-74: EPA needs to incorporate the group-specific parameter data, not currently listed.

- All Appendices: Based on its response to comments, EPA must update and detail the supporting assessments in the Appendices for both consistency and accuracy.

LITERATURE REVIEW/ANALYSIS: NASA identified specific gaps in the known supporting literature, varying from inconsistent presentation of documented literature to omission of significant reference literature. Review of the draft also presented a sizable literature review but no systematic review or analysis of the wealth of literature. Specific examples include:

- Section 4.0, Pages 207-240: NASA identifies several examples of literature not referenced or key findings not discussed.

- Section 4.3, Page 391, 392: EPA assumes all the negative result studies to be impacted by non-differential classification but provides no systematic support for this assumption. In addition, EPA utilizes PMR studies and semi-qualitative assessment that lack the complete cohort and are therefore are not appropriate or complete enough to estimate risk (this issue is noted elsewhere in the draft).

- Appendix B: The discussion in Appendix B does not provide EPA's criteria for choosing specific literature nor explanation of the scientific study question to be answered. EPA provides a sizable body of literature that may be comprehensive but this effort is not systematic. Choice of literature must support the basic study question and criteria to use or exclude specific studies can have a profound effect on the results of the risk assessment. The draft lacks this clarifying information and statement of the scientific study question.

- EPA does not include concordant research and analysis presented in the Institute of Medicine (IOM) report on its categorization scheme to evaluate epidemiological data, "Gulf War and Health, Vol. 2, Insecticides and Solvents", National Academy Press (2003) or the NAS report, "Contaminated Water Supplies at Camp LeJeune; Assessing Potential Health Effects (2009). The NAS report states that its charge is not regulatory risk assessment but to be, "in the present case, however the goal is not prevention of risk, but rather the use of the best available data to categorize evidence for a relationship between a chemical exposure and the occurrence of an adverse health outcome in humans". It is important to note that both the NAS and the IOM reports address specific technical issues directly related to and supportive of EPA's draft risk assessment efforts for TCE. These NAS reports present differing findings from the EPA draft on health effects due to TCE exposure, robustness and conclusions of the existing literature, reproductive impacts, and cancer potential specific to TCE.

- EPA did not review or cite specific examples of referenced papers in the field, such as Moore Martha M. et al, "Analysis of in vivo mutation data can inform cancer risk assessment", Regulatory Toxicology and Pharmacology, (2008) or Corton, J. Christopher, "Evaluation of the Role of Peroxisome Proliferator- Activated Receptor alpha (PPAR alpha) of Mouse Liver Tumor Induction by TCE and Metabolites", Critical Reviews in Toxicology, Informa (2008). These papers address specific technical issues fundamental to EPA's assessment such as interspecies

comparisons and Mode of Action (MOA). These examples include papers from EPA NCEA scientists.

- All Appendices: Based on its response to comments, EPA must update and detail the supporting reviewed and applied literature in the Appendices for both consistency and accuracy.

CARGINOGENICITY/ MODE OF ACTION (MOA): EPA provided a lengthy literature review in support of estimating potential TCE cancer risk. However, the depth of the literature search is not evaluated through a meta-analysis is needed that clarifies the relative strengths and weaknesses or EPA's assumptions. Due to the size and complexity of the draft risk assessment, meta-analysis is necessary to address significant questions on the impact of confounding factors and data limitations. Selected examples that highlight this issue include:

- Section 4.3, Pages 395, 399: EPA states several assumptions, such as that it is unlikely that TCE exposure and smoking are related and that the cited literature is robust. These assumptions are not substantiated nor are the specific identified weaknesses in the data (i.e. exposure assessment limitations, confounding).

- Section 4.3.3., Page 423: EPA provides mixed results on the role of VHL mutation, TCE exposure and the relationship to kidney cancer, making it difficult for the reader to understand EPA's conclusions. Elsewhere in the section 4.3.3 and in the draft, EPA bases the MOA determination on the causal relationship between chemical exposure and mutation but does not address that this may not be a sufficient condition to assume causality.

- Section 4.3.4: EPA cites the low incidence of kidney tumors in rats (based on the 1990 NTP study) as the basis for its conclusions without additional supporting data addressing the limitations and requirements of using historic controls (i.e. gender, strain, year, etc.). EPA's reliance on this data necessitates substantiation and clarification of use of these studies to ensure accuracy that is not found in the current draft.

- Section 4.3.5 and Section 6: EPA's reliance on the NTP studies (1998 and the 1990 Male Rat Study) does not include an analysis of the limitations in these studies in its discussion of kidney and liver cancer risks. The 1988 NTP study of four strains stated that the studies were, "inadequate studies of carcinogenic activity because of chemically- induced toxicity, reduced survival and the deficiencies in the conduct of the study" and then states, "...for these reasons, these studies were considered inadequate to evaluate the presence or absence of carcinogenic potential of TCE."

- Section 4.3.5 and Section 6: The 1990 NTP male rat study also presents significant limitations not discussed in the draft. NTP conducted that study only on male rats at very high doses that left only 17 animals surviving through the experiment. The high doses, greater than the MTD, lead both EPA and NTP to state that the impact of high doses did not yield clear results on the potential for tumors. The draft does not characterize these limitations or how such limitations

- Section 4.3.5 and Section 6: Following on the need for clarification of study limitations and inadequacies listed above in use of the NTP studies, the integration of the various studies to determine the kidney cancer risk also raises significant concerns over the lack of discussion on the studies' limitations and uncertainties. Examples include a study with identification of one statistically significant response out of over 90 chronic-dosed groups of male and female rats and mice when such a singular response is expected statistically to occur with no relationship to a specific chemical exposure. This limitation is not discussed.

- Section 4.3.5: EPA does not consistently provide data on from the identified literature that does not demonstrate an increased kidney cancer risk. Comparison between the Tables 4.3.6- 4.3.10 identified key information and conclusions from the studies in the text did not match the information provided in the Tables, creating confusion for the reader and raising questions on EPA's conclusion. As written, the draft discussion does not explain or substantiate EPA's conclusion on the relationship between TCE exposure and kidney cancer risk, especially in light of the consideration of study limitations, uncertainties and clear association linking exposure and cancer risk. Outstanding questions, such as whether PPARalpha agonism is an MOA and whether it corresponds to key events and meets the criteria to be sufficient to determine carcinogenicity, is not addressed and represent a weakness in the draft (also noted in Section 4.4.7).

- Section 4.3.7: EPA's determination of the mutagenic Mode of Action (MOA) does not clearly provide the hypothesis for the sequence of key events, the pathways for the primary MOA and any subsequent MOAs. Such a pathway is necessary to determine dose-response and temporal relationships and to ensure the appropriate consideration of tumors that occur after the exposure and not before. Determination of the MOA endpoint and related data are required to support the estimation of linear impacts in response to dose. The draft lacks clear substantiation or discussion of the supporting information, raising the significant questions of what technical support EPA has to assume a linear dose response relationship.

- In addition, EPA's draft guidance (US EPA (2007) Framework for determining a mutagenic mode of action for carcinogenicity (external review draft) EPA 120/R-07/002-A) states that such pathways contain data to demonstrate a progression of events. EPA's draft guidance also states that genotoxicity assays (in vivo and in specific in vitro), positive results are not sufficient to identify the MOA. NASA notes that while the EPA guidance is draft, it details clear scientifically-based direction on how use a range of studies to characterize the MOA.

- Sections 4.3.7, 4.4.6, and 4.4.7: EPA does not provide a supporting Human Relevance Framework and key events tables detailing dose response and temporal concordance to array the supporting information, making it difficult for the reader to understand the relative

strengths, weaknesses, and data gaps, outstanding uncertainties in the estimation of the MOA for either kidney or liver cancer. EPA also does not address issues and potential limitations of the previously identified current literature raised in the IOM (1993), NAS (2009) reports, Moore, M. M., et al (2008) or Corton (2008).

- Section 4.5, Pages 626-628, 634: Specific text in the draft require clarification or correction in the interpretation of selected studies including: designation of seven cohort studies that do not contain job exposure matrices, only the broad designation of "TCE facility" which likely include workers with little or no TCE exposures; two different groups of studies designated "high quality" are based on self-reporting and therefore subject to bias and not statistically significant; and inclusion of an ATSDR PMR analysis, without identification of study limitations, which focused on a subset of deaths report and does not meet threshold criteria of an epidemiological study. As written, these studies without discussion of their respective limitations are accorded greater weight than appropriate.

- Section 4.5.2.4, Page 683-686: The discussion evaluating specific studies into the relationship between TCE exposure and malignant lymphoma, cancers of the immune system, and lung cancer requires editing and correction. Limited study results relate documented cancer incidence with TCE exposure. Identification and consideration of the limitations, uncertainties, and results (such as statistical significance and decreases, not increases of incidence) of the identified studies are not presented. Additionally, cancer of the immune systems' data is incorrectly listed as being in Tables 4.5.9 and 4.5.10. but is found in Tables 4.5.11 and 4.5.12, necessitating correction in the draft text.

- Section 4.6.2.2: EPA's determination, based on one statistically significant result for one species (mouse), among the studies considered, that "…the overall results are consistent with TCE causing mild increase in pulmonary tumor incidence in mice" requires re-evaluation and clarification. The results of that one statistically significant finding in that one study on mice provides a very limited, equivocal result and requires additional substantiation to support that TCE exposure causes lung tumors in mice.

- Section 4.10.2, Page 979: EPA's determination of TCE as a carcinogen by all routes does not meet the requirements established by EPA (US EPA, (2005), Guidelines for Carcinogenic Risk Assessment). EPA's Guidelines (2005) require designation of "cancerous to human" must demonstrate strong epidemiological evidence of a causal association in humans. Criteria include strong evidence of an association between human exposure and cancer (or precursors to cancer), significant levels of evidence of carcinogenicity in animals, MOA's for carcinogenicity and precursor events identified for animals, and supporting evidence that precursor events in animals also occur in humans. NASA's review of the EPA Guidelines (2005) indicate that the TCE studies lack clear causal evidence and conform to the designation of "suggestive" evidence of cancer. EPA Guidelines (2005) for the designation of "suggestive" evidence includes: small effects observed, findings of small effects in tumors with high background rates that can be

attributed to known or unknown factors, and studies with positive results also exhibit limitations (i.e. study power, design or conduct) that negatively impact on the ability to determine confident, supported conclusions. Based on the information provided by EPA on TCE, the designation of "suggestive" is the most appropriate designation, in keeping with EPA Guidance.

- Section 5.2.2: The draft does not adequately substantiate, based on the available biological data that the MOA is established for TCE or a clearly linear dose relationship is present. EPA needs to clearly state if it is assuming linear extrapolation is a default and the basis for this assumption.

- Section 6.0: EPA's discussion of TCE exposures and cardiac abnormalities relies on a very limited set of studies without delineation of identified limitations and the nature of the date set. EPA acknowledges the weakness of this set of studies (pages 855-857) but then states the animal data is "strong, but not unequivocal, evidence". EPA is encouraged to support its decision to use this animal data and address confusion in the text over the applicability of the data used and supporting assumptions.

- All Appendices: Based on its response to comments, EPA must update and detail the supporting assessments in the Appendices for both consistency and accuracy.