Draft Charge to National Academy of Sciences Panel for the Toxicological Review of Tetrachloroethylene
April 24, 2008

The U.S. Environmental Protection Agency (EPA) is seeking a National Academy of Sciences (NAS) review of the scientific basis supporting the human health assessment of tetrachloroethylene that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by the EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD).

Tetrachloroethylene is a solvent used for cleaning clothes and for metal cleaning and degreasing. EPA undertook the current draft health assessment with the aim of reviewing and evaluating the non-cancer and cancer health effects of tetrachloroethylene.

This draft Toxicological Review includes a chronic Reference Concentration (RfC) and carcinogenicity assessment, which are not currently available on IRIS, as well as an update of the 1988 IRIS Reference Dose (RfD). The overall goal of this NAS review is to seek input on (1) the evaluation of scientific evidence regarding the health effects of tetrachloroethylene and (2) the application of such data in the associated quantification of human health risks. Below is a set of charge questions that address the scientific and science policy issues in the assessment of tetrachloroethylene. Please provide detailed, specific explanations for responses to the charge questions.

We are also particularly interested in seeking advice from the Committee on the adequacy of the quantitative uncertainty and sensitivity analyses and the manner in which this information is discussed, interpreted, and presented. Our attempts to characterize uncertainty in this assessment are in direct response to comments and recommendations from other NAS/National Research Council Committees[1] and the Agency's Science Advisory Board[2] regarding EPA's characterization of uncertainty, particularly the need to consider the full range of plausible data sets, modeling approaches, and parameter values and present alternative risk estimates in EPA's chemical assessments. In addition, EPA's "transparency goals" described in its 2000 Risk Characterization Handbook (See Attachment 1) direct assessments to present all assumptions, extrapolations, models, and choices and the impact of these (and alternatives) on the results of the assessment.

[1] NAS in its 2006 evaluation of EPA's Dioxin Reassessment; by NAS in its 2006 evaluation of EPA's assessment of the Human Health Risks of Trichloroethylene
[2] SAB's 2007 draft review of EPA's draft assessment of the carcinogenicity of ethylene oxide

Another important issue we would like the Committee to comment on is whether the various default approaches that are used in the draft tetrachloroethylene assessment are reasonable and provide the best characterization of risk. In particular, the assessment often cites default approaches[3] that are discussed in EPA's 2005 Guidelines for Carcinogen Risk Assessment[4]. The Guidelines state:

> "Rather than viewing default options as the starting point from which departures may be justified by new scientific information, these cancer guidelines view a critical analysis of all of the available information that is relevant to assessing the carcinogenic risk as the starting point from which a default option may be invoked if needed to address uncertainty or the absence of critical information."

While noting that "EPA believes that the cancer guidelines represent a sound and up-to-date approach to cancer risk assessment, and the cancer guidelines enhance the application of the best available science in EPA's risk assessments," the 2005 Guidelines also state "Use of the cancer guidelines in future risk assessments will be based on decisions by EPA that the approaches are suitable and appropriate in the context of those particular risk assessments. These judgments will be tested through peer review, and risk assessments will be modified to use different approaches if appropriate."

[3] The 2005 Guidelines for Carcinogen Risk Assessment defines the term as "Default options are inferences based on general scientific knowledge of the phenomena in question and are also matters of policy concerning the appropriate way to bridge uncertainties that concern potential risk to human health."

[4] US EPA. 2005. Guidelines for carcinogen risk assessment and supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. Federal Register 70 (66):17765-17817.

General Charge Questions:

1. Is the Toxicological Review logical, clear, and concise? Does EPA provide a sound, scientifically balanced, and objective review and synthesis of the key scientific evidence for noncancer and cancer hazard?
2. Please identify any additional important studies that should be considered in the assessment of the noncancer and cancer health effects of tetrachloroethylene.

Specific Charge Questions:

(A) Non-cancer assessment

1. Selection of neurotoxicity as the basis for the RfC and RfD for tetrachloroethylene.

A number of studies assessing neurobehavioral and other effects in both humans and rodents are available for RfC and RfD analysis.

a. Is EPA's selection of the specific neurotoxicity critical effect of visual dysfunction and cognitive deficits that are used to develop non-cancer reference values appropriate? Based on the scientific evidence, are there other (adverse) endpoints that would occur at lower or higher exposures that are equally or more justifiable that should be used (either in lieu of or in addition to the neurotoxicity effects) to develop the RfC or RfD?

b. Please comment on the rationale for the selection of the principal study.

    1) Does EPA provide a clear set of criteria for evaluating the various human and animal studies and provide a scientifically defensible rationale for selecting the Altmann *et al.* study as the "principal study" in development of non-cancer reference values? Are there other studies that are equally or more justifiable based on the scientific evidence that should be used (either in lieu of or in addition to the Altmann *et al.* study) to develop the RfC or RfD?

    2) Does EPA provide a clear and comprehensive description of the potential limitations of the Altmann *et al*. study (*e.g.*, small sample size, matching of controls to exposed subjects, *etc*.)? Is EPA's use of this study to develop the RfC and RfD appropriate in light of these limitations and the limitations of other epidemiologic and toxicological studies?

    3) Is EPA's use of route extrapolation for developing an RfD from a study of inhalation exposure by Altmann *et al*. appropriate and consistent with pharmacokinetic and toxicological data on tetrachloroethylene?

    4) Are there other (either oral or inhalation exposure) studies that are equally or more justifiable based on the scientific evidence that should be used (either in lieu of or in addition to route extrapolation from the Altmann *et al.* study) to develop the RfC or RfD?

2. Characterization of uncertainties.

The non-cancer assessment considers uncertainty based on extrapolation from laboratory animals to humans, variations in response within experimental species, human variation, and database deficiencies. The non-cancer RfC and RfD values are based on a specific neurotoxicity effect. EPA also presents reference values based on other effects to illustrate the dose dependency of the multiple observed toxicities.

a. Has EPA accurately and clearly characterized critical data gaps and uncertainties and the bases for selection of uncertainty factors for the RfC and RfD? Please comment on the rationales underlying the choice of uncertainty factors, and specifically the database uncertainty factor, which is intended to account for the degree of limitations in both human and animal data.

b. Does EPA adequately present the use of all assumptions, choices, extrapolations, and models and their impact on the assessment in its discussion of the development of the non-cancer risk values? Is the level of uncertainty associated with the RfC and RfD adequately characterized and presented?

c. EPA concludes that "A quantitative characterization of the uncertainty in the RfC and RfD for tetrachloroethylene is not feasible because of the varied nature of the available database and the limited data available for many of the studies" (Section 6.2.1.2). Does the Committee agree with this conclusion? Does the Committee have suggestions for ways to quantitatively characterize these uncertainties and which studies or other data may be amenable for such an analysis?

d. What advantages and disadvantages does EPA's method of presenting reference values based on multiple toxic effects have compared with the conventional approach of presenting reference values for only the critical effect? Please comment on EPA's graphical presentation of non-cancer reference values that could have been derived from studies of different neurotoxic effects or toxic effects in other organ systems, which aims to show the range of tetrachloroethylene concentrations at which different effects occur. Is this information appropriately used or considered in EPA's characterization of the RfC and RfD?

(B) Cancer assessment

1. Weight of evidence descriptor.

The assessment concludes that tetrachloroethylene is "likely to be carcinogenic to humans" by all routes of exposure, within the framework of the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a).

a. Does EPA provide a clear and cogent weight of evidence evaluation? Does the assessment support the conclusion that tetrachloroethylene is likely to be carcinogenic to humans via the oral and inhalation routes of exposure (at all levels of exposure)?

b. Is the "likely" descriptor appropriately described? For example, EPA states "Although the term "likely" can have a probabilistic connotation in other contexts, its use as a weight of evidence descriptor does not correspond to a quantifiable probability of whether the chemical is carcinogenic." and concludes "In summary, use of the weight of evidence descriptor 'likely to be carcinogenic to humans' for tetrachloroethylene is intended to communicate that the available information indicates the presence of a human health hazard." Does the Committee agree with this characterization of this descriptor?[5]

c. Are the quantitative implications of the "likely" descriptor adequately described? Should the assessment acknowledge that the predicted cancer risk could be zero (e.g., if the animal bioassay response data are not relevant for humans, there is no casual relationship between tetrachloroethylene and cancer)?

2. Mode of action considerations.

The mode of action of a carcinogen can inform identification of hazards and approaches used for dose-response. The assessment concludes that for tetrachloroethylene, a mode of action has not been definitively established for any of the site-specific tumor types.

a. Does EPA's draft assessment of tetrachloroethylene accurately and clearly evaluate information on mode of action? Are the conclusions about mode of action for the cancer endpoints scientifically defensible and appropriate?

b. Do the available data support the hypothesis that multiple modes of action may contribute to carcinogenesis following exposure to tetrachloroethylene?

c. Does EPA provide a full characterization of the data gaps related to the mode of action and the implications for the characterization of risk? Does the committee have suggestions for future studies to address data gaps related to the mode of action and the characterization of risk?

d. Does EPA clearly and objectively describe the low-dose extrapolation approach (*i.e.*, linear extrapolation in accordance with default recommendations in the EPA 2005 *Guidelines for Carcinogen Risk Assessment*)? Do the mechanistic data, which for example EPA determines are insufficient to conclude that a mutagenic MOA can be established, support the use of other plausible low-dose extrapolation models (either in lieu of or in addition to linear low-dose extrapolation) to characterize cancer risk?

[5]EPA's (2005) Cancer Guidelines states that the descriptor "Likely to Be Carcinogenic to Humans" is appropriate when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "Carcinogenic to Humans."

e. EPA concludes "A key consideration in clarifying how risks should be estimated for low-dose exposure is the MOA" but also concludes "The extent to which the overall uncertainty in low-dose risk estimation could be reduced if the MOA for tetrachloroethylene were known with a high degree of confidence is of interest, but clear data on the MOA of tetrachloroethylene is not available, and even if it were, incorporation of MOA into dose-response modeling might not be straightforward and might not significantly reduce the uncertainty about low-dose extrapolation. This is because the mode of action as well as other factors, especially human response variability, are determinants of the dose-response function in humans." Does the Committee agree with EPA's conclusions about the usefulness of MOA data in addressing and characterizing uncertainties in low-dose risk estimation?

f. Does EPA clearly address why age-dependent adjustment factors for cancer risk are not applied, according to the EPA 2005 *Guidelines for Carcinogen Risk Assessment* and *Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens*?

3. Development of the inhalation unit risk and oral slope factor based on the male rat leukemia data in the JISA study and a linear low-dose extrapolation approach.

A number of studies, endpoints, sex/species combinations and low-dose extrapolation approaches are available for analysis of cancer risk. EPA's concluding unit risk estimate[6] relies on choices of tumor type, point of departure, and low-dose extrapolation approach that aim to provide a "reasonable upper bound estimate" of risk. Because the assessment judged that there was no basis for preferring one PBPK model over another, a range of tetrachloroethylene unit risk estimates calculated using three PBPK models is given.

a. Is EPA's selection of mononuclear cell leukemia found in male rats from the JISA study appropriate for characterizing the inhalation unit risk and oral slope factor? Are there other studies, endpoints, or sex/species combinations that are equally or more justifiable based on the scientific evidence that should be used (either in lieu of or in addition to those selected) to estimate cancer risk?

b. Is EPA's use of the multi-stage model to derive the point of departure in developing the inhalation unit risk and oral slope factor appropriate? Are there other approaches that should be used (either in lieu of or in addition to this approach) to estimate cancer risk?

c. Does EPA provide a clear and scientifically defensible rationale for using a default, linear low-dose extrapolation approach to calculate the inhalation unit risk and oral slope factor? Does the Committee agree with EPA's justification for low-dose

[6] Defined in the IRIS glossary (see http://www.epa.gov/iris/gloss8.htm) as "the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/L in water, or 1 µg/m3 in air". Upper bound is defined as "a plausible upper limit to the true value of a quantity. This is usually not a true statistical confidence limit."

linearity (Section 6.2.2.2 - *(2) Choice of low-dose extrapolation approach*)? Do the assumptions presented by EPA support the use of the default approach (e.g., does additivity to background imply linearity from the POD to the origin)? Are there other low-dose extrapolation models that are equally or more justifiable based on the scientific evidence that should be used (either in lieu of or in addition to the default approach) to inform risk managers?

d. Is EPA's use of the word "plausible" to describe the upper bound unit risk estimates appropriate and consistent with EPA guidance, or would another term (such as "reasonable") be more appropriate? For example, the Cancer Guidelines use these two terms in the following contexts:

> "Moreover, the absence of tumors in well-conducted, long-term animal studies in at least two species provides **reasonable** assurance that an agent may not be a carcinogenic concern for humans."
>
> "In constructing high end estimates of risk, the assessor should bear in mind that the high-end risk is a **plausible** estimate of the risk for those persons at the upper end of the risk distribution ..."

4. Consideration of uncertainties.

The cancer assessment considered the contribution of a number of sources of uncertainty. Some uncertainties (*e.g.*, pertaining to mode of action and human sensitivity and variability) were qualitatively expressed, while in other cases, EPA examined the potential quantitative impact on the risk estimate. In addition to the unit risk estimate, the assessment also provides lower bounds (e.g., confidence limits) as well as central estimates.

a. Has EPA appropriately identified and described the key sources of uncertainty in assessing cancer risks from tetrachloroethylene?

b. Has EPA transparently and soundly characterized the qualitative significance, and where possible, the quantitative magnitude of uncertainties in the low-dose cancer risk estimates for humans? To what extent are these characterizations informative of the human carcinogenic risk of tetrachloroethylene? Does the Committee have suggestions for more completely evaluating these two types of uncertainties to better inform the tetrachloroethylene risk assessment?

c. Does EPA adequately present the use of all assumptions, choices, extrapolations, and models and their impact on the assessment in its discussion of the development of the cancer risk values? Does the assessment clearly and objectively present and support the choices made in developing upper bound estimates of cancer risk for tetrachloroethylene? Are there other "plausible" or "reasonable" upper bound estimates that are equally or more justifiable? Are EPA's estimates of the central and lower bound risk values (using the default extrapolation approach) appropriately developed and presented?

d. What advantages and disadvantages does EPA's method of presenting cancer risk values based on multiple endpoints or sex/species combinations have compared with the conventional approach of presenting cancer risk values for only the most sensitive response? Please comment on EPA's tabular presentation of risk values calculated from other datasets [see Tables 6-2, 6-3, 6-4 and 6-5]. Is the information presented on values derived from other datasets appropriately used, interpreted, or considered in EPA's characterization of the unit risk and cancer slope factor?

e. In regards to its presentation of cancer risk values for leukemias in male rats based on different low-dose extrapolation approaches (Section 6.2.2.2 - *(2) Choice of low-dose extrapolation approach*), EPA concludes "With such large spreads in confidence intervals, the extrapolated models in effect provide little information about actual low-dose risks. These results are not presented as the basis for alternative estimates of human risk, as they are not judged to provide sound or useable scientific estimates for the compound-specific risks from tetrachloroethylene." EPA further concludes that the "other approaches to estimate upper bounds on risk were not considered informative for risk estimation" and these estimates "would not provide plausible upper bounds on risk given the available data." Does the Committee agree with these conclusions? Does the Committee have any suggestions for how to use or interpret these results? How informative are the estimates of male rat cancer risk, which are presented in units of $(\text{mg-eq/kg-day})^{-1}$corresponding to 1.5×10^{-5} mg-eq/kg-day internal dose in rats, for evaluating the potential range of human cancer risk? Would it be more informative to provide cancer risk estimates similar to those presented in Table 6-3?

f. Please discuss research areas likely to reduce the uncertainties in future tetrachloroethylene cancer risk assessments.

(C) Choice of dose metrics for various toxic outcomes, PBPK modeling and interspecies scaling approaches.

Exposure to tetrachloroethylene results in the production of several metabolic products. The parent compound is used as the dose metric for neurotoxic effects and the rate of formation of total metabolites in humans is used for cancer effects. Metabolite formation was modeled using three different PBPK models, leading to a range of cancer risk factors.

1. Please comment on the use of route extrapolation for developing an RfD from a study of inhalation exposure.

2. Please comment on the sufficiency of the available data to identify whether the parent compound and/or specific metabolites are responsible for the induction of cancer from tetrachloroethylene exposure.

3. Has EPA clearly and objectively presented in a scientifically defensible manner:
   a. the choice of dose metrics for different outcomes, and their use in PBPK models?
   b. the strengths and weaknesses of different modeling approaches?

c. the approach employed in deriving the toxicologically equivalent human dose, including the application of a $BW^{3/4}$ interspecies scaling factor to the fraction of the administered rodent dose that is metabolized?

4. Is EPA's judgment that there is not a strong basis for preferring any one of the PBPK models over other available models for use in the risk assessment reasonable and scientifically defensible?

ATTACHMENT I

Transparency

Transparency provides explicitness in the risk assessment process. It ensures that any reader understands all the steps, logic, key assumptions, limitations and decisions in the risk assessment, and comprehends the supporting rationale that lead to the outcome. Transparency achieves full disclosure in terms of:

a) the assessment approach employed
b) the use of assumptions and their impact on the assessment
c) the use of extrapolations and their impact on the assessment
d) the use of models *vs*. measurements and their impact on the assessment
e) plausible alternatives and the choices made among those alternatives
f) the impacts of one choice *vs*. another on the assessment
g) significant data gaps and their implications for the assessment
h) the scientific conclusions identified separately from default assumptions and policy calls
i) the major risk conclusions and the assessor's confidence and uncertainties in them
j) the relative strength of each risk assessment component and its impact on the overall assessment (*e.g.,* the case for the agent posing a hazard is strong, but the overall assessment of risk is weak because the case for exposure is weak)

Source: Science Policy Council Handbook: Risk Characterization (2000) EPA 100-B-002