Revised Charge to National Academy of Sciences Panel for the
Toxicological Review of Tetrachloroethylene
February 9, 2009

The U.S. Environmental Protection Agency (EPA) is seeking a National Academy of Sciences (NAS) review of EPA's 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 chronic 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 chronic Reference Dose (RfD). The overall goal of this NAS effort is to obtain a scientific peer review of EPA's (1) evaluation of scientific evidence regarding the health effects of tetrachloroethylene and (2) application of such data in the associated quantification of human health risks. EPA is seeking this review to aid the Agency in expeditiously completing the tetrachloroethylene IRIS assessment, and thus to provide a practical risk assessment for risk managers addressing ongoing decision making needs for environmental exposures to tetrachloroethylene.

EPA has developed this draft risk assessment in the context of the Agency's existing guidance for risk assessment, and in particular EPA's 2005 Guidelines for Carcinogen Risk Assessment and guidance for reference value based assessments (RfC's and RfD's). EPA's risk assessment guidance documents have been developed through processes incorporating extensive Agency deliberations and external peer review. It is EPA's intent that the tetrachloroethylene risk assessment reflects the framework and broadly applicable science judgments incorporated into this guidance. EPA guidance stresses the importance of sound science analysis and judgment and is not intended to provide a rigid prescription for the conduct of specific risk assessments. As expressed in the EPA cancer guidelines, "The primary goal of EPA actions is protection of human health; accordingly, as an Agency policy, risk assessment procedures, including default options that are used in the absence of scientific data to the contrary, should be health protective." (See documents on EPA's IRIS web site http://www.epa.gov/iris , including: http://www.epa.gov/ncea/iris/RFD_FINAL[1].pdf , and http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283)
With this NAS review, EPA's priority is to obtain advice specific to the risk assessment of tetrachloroethylene and its consistency with EPA guidelines.

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.

General Charge Questions:

1. Does the Toxicological Review provide a scientifically sound, balanced, and transparent review and synthesis of the key scientific evidence for chronic noncancer and cancer hazard and risk?

2. Please identify any additional important studies that should be considered in the assessment of the chronic non-cancer 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 neurotoxicity, and specifically the outcomes of visual dysfunction and cognitive deficits, appropriate for providing a point of departure for derivation of the RfC and RfD? The goal of a reference value is to provide an estimate of exposure to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime.

   b. Does EPA provide a sound and transparent description of the relevant studies on the neurotoxic effects of tetrachloroethylene?

   c. Does the assessment present an appropriate rationale for selection of Altmann *et al.* as the critical study? If another study is judged more appropriate for use as the critical study, please provide a critical evaluation of that study and its suitability in meeting the goals of a reference value.

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 the basis for selection of uncertainty factors for the RfC and RfD? Please comment on the rationales underlying the choice of uncertainty factors, such as the database uncertainty factor, which is intended to account for the degree of limitations in both human and animal data.

b. 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.

(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?

b. 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)?

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 provide a sound evaluation and characterization of the available data related to mode(s) of action for the carcinogenicity of tetrachloroethylene?

b. Do the available data support EPA's conclusion that mode(s) of action for tetrachloroethylene-induced carcinogenesis is unknown?

c. 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.

EPA's draft unit risk estimate[1] 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 draft assessment judged that there was no strong basis for preferring one PBPK model over

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[1]   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."

another, a range of tetrachloroethylene unit risk estimates calculated using three PBPK models is given.

  a. Please comment on EPA's selection of mononuclear cell leukemia in male rats from the JISA study for quantitative derivation of the inhalation unit risk and oral slope factor. Note that, consistent with EPA's 2005 Guidelines for Cancer Risk Assessment, the draft assessment does not infer site concordance of tumors across species. If another study or endpoint is judged more appropriate for the derivation of these risk values, please provide a critical evaluation of that endpoint and its suitability for supporting a unit risk estimate.

  b. 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*)?

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 identified and described the key sources of uncertainty in assessing cancer risks from tetrachloroethylene?

  b. Is this analysis transparent and presented at a suitable level of detail for this IRIS assessment?

  c. Does the assessment clearly and objectively present the choices made in developing reasonable upper bound estimates of cancer risk for tetrachloroethylene?

  d. The assessment includes tabular presentations of point of departure (POD) based analyses using different endpoints and approaches [see Tables 6-2, 6-3, 6-4 and 6-5]. Is the information clearly presented and appropriately characterized?

  e. In Section 6.2.2.2, the assessment presents exploratory calculations of potential probabilities of tumor response at low dose using different functional forms. Is this analysis clearly presented and appropriately characterized?

  f. Please discuss research areas likely to better characterize 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 PBPK application for route-to-route extrapolations in developing an RfD and an oral slope factor from studies 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:

    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 conclusion that there is not a strong basis for preferring any one PBPK model for use in the risk assessment soundly and transparently characterized?