Charge to External Peer Reviewers for the
IRIS Toxicological Review of Trichloroethylene (TCE)
May 2009 DRAFT

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of TCE 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).

An IRIS assessment for TCE was posted to the database in 1985 and withdrawn in 1989 due to uncertainties with respect to the classification for TCE carcinogenicity. In 2000, a monograph comprising 16 articles on the "State-of-the-Science" on TCE health risks was published in Environmental Health Perspectives[1]. EPA synthesized the information from these studies to develop an external review draft *Trichloroethylene Health Risk Assessment: Synthesis and Characterization*[2], released in August 2001 . This 2001 draft was subject to peer review by an independent panel of the EPA Science Advisory Board (SAB). In December 2002, the SAB published its peer review report in *Review of Draft Trichloroethylene Health Risk Assessment: Synthesis and Characterization: An EPA Science Advisory Board Report*[3]. In addition, the public submitted more than 800 pages of comments to EPA during a 120-day public comment period. In February 2004, EPA held a public symposium on new TCE science in which a number of authors of recently published scientific research presented their findings.[4] Due to continuing scientific issues as well as emerging significant new science, EPA, along with the Department of Defense, Department of Energy, and the National Aeronautics and Space Administration, cosponsored a consultation on TCE science issues with an expert panel convened by the National Academy of Sciences (NAS) Board on Environmental Studies and Toxicology. EPA developed four issue papers, presented to the NAS panel, highlighting important scientific issues related to TCE[5]. EPA scientists subsequently published a mini-monograph on these TCE science issues in Environmental Health Perspectives.[6] In 2006, the NRC released its report *Assessing the Human Health Risks of Trichloroethylene:Key Scientific Issues*[7].

The current external review draft TCE health assessment reviews the available scientific literature on the human health effects of TCE, considering the input and advice from all the above sources, in addition to following the general guidelines for risk assessment set

[1] *Environmental Health Perspectives.* Vol 108, Suppl 2, May 2000.
[2] EPA/600/P-01/002A, available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23249.
[3] Available at <http://www.epa.gov/sab/pdf/ehc03002.pdf>
[4] Symposium presentations and a transcript are available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=75934.
[5] Available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=117502.
[6] *Environmental Health Perspectives.* Volume 114, Number 9, September 2006.
[7] Available at http://www.nap.edu/catalog.php?record_id=11707.

forth by the NRC in 1983[8] and numerous guidelines and technical reports published by EPA (see Chapter 1 of the assessment). Specifically, this IRIS assessment provides an overview of sources of exposure to TCE, reviews the data on the toxicokinetics of TCE and its metabolites, describes the development of an updated physiologically-based pharmacokinetic (PBPK) model of TCE and metabolites, characterizes the hazard posed by TCE exposure for carcinogenicity and non-cancer health effects based on the available scientific literature, and assesses the dose-response for TCE health effects by deriving a chronic Reference Dose (RfD) and chronic Reference Concentration (RfC) for non-cancer effects and an inhalation unit risk and oral unit risk for carcinogenic effects.

Charge Questions

Below is a set of charge questions that address scientific issues in the assessment of TCE. Please provide detailed explanations for responses to the charge questions. All comments should give consideration to the urgent need of EPA regions and programs, and state and local governments for a completed TCE assessment. Therefore, recommendations for changes or additional analyses should focus on those that would make a significant impact on the accuracy, objectivity, transparency, or utility of EPA's qualitative or quantitative conclusions.

1. Has EPA logically, accurately, clearly, and objectively represented and synthesized the scientific evidence supporting its hazard characterization of TCE human health effects? Are there changes to EPA's conclusions, their rationale, or their presentation that should be considered that would make a significant impact on the accuracy, objectivity, transparency, or utility of the TCE assessment? Specifically, is there adequate support for EPA's evaluation and conclusions as to:
    a. TCE non-cancer effects;
    b. TCE carcinogenicity;
    c. The role of metabolism in TCE carcinogenicity and non-cancer effects;
    d. The mode(s) of action (MOA(s)) of TCE carcinogenicity and non-cancer effects, including the conclusion that the weight of evidence supports a mutagenic MOA for TCE-induced kidney tumors; and
    e. The factors, including genetics, lifestage, background and co-exposures, and pre-existing conditions that could modulate susceptibility to TCE carcinogenicity and non-cancer effects.

2. Is EPA's updated PBPK model for TCE and its metabolites clearly and transparently described, and technically adequate for supporting EPA's hazard characterization and dose-response assessment? Are there changes to the PBPK model structure, parameter calibration, evaluation, or predictions that should be considered that would make a significant impact on the accuracy, objectivity, transparency, or utility of EPA's qualitative or quantitative conclusions?

[8] NRC (1983). *Risk Assessment in the federal government: managing the process.* Washington DC: National Academy Press.

3. Is EPA's updated meta-analysis of the epidemiologic data for TCE and kidney cancer, non-Hodgkin's lymphoma, and liver cancer clearly and transparently described, and technically adequate for supporting EPA's hazard characterization and dose-response assessment? Are there changes to the study selections or analysis methods that should be considered that would make a significant impact on the accuracy, objectivity, transparency, or utility of EPA's qualitative or quantitative conclusions?

4. Is the dose-response assessment for non-cancer effects clearly and transparently described, and adequately justified to support EPA's draft RfC and RfD? Are there changes in the non-cancer dose-response analyses that should be considered that would make a significant impact on the accuracy, objectivity, transparency, or utility of EPA's quantitative conclusions? Specific issues to address include:
    a. The process used for screening and identifying candidate critical effects studies and effects;
    b. Development of points-of-departure, including benchmark dose modeling (e.g., selection of dose-response models, benchmark response levels);
    c. Selection of PBPK-based dose metrics for inter-species, intra-species, and route-to-route extrapolation, including the use of body weight to the ¾ power scaling for some dose metrics;
    d. Selection of uncertainty factors;
    e. Development of equivalent doses and concentrations for sensitive humans from PBPK modeling to replace standard uncertainty factors for inter- and intra-species toxicokinetics, including selection of the 99^{th} percentile for overall uncertainty and variability to represent the toxicokinetically-sensitive individual;
    f. Characterization of uncertainty and variability;
    g. The selection of NTP (1988) [toxic nephropathy], NCI (1976) [toxic nephrosis], Woolhiser et al. (2006) [increased kidney weights], Keil et al. (2009) [decreased thymus weights and increased anti-dsDNA and anti-ssDNA antibodies], Peden-Adams et al. (2006 [developmental immunotoxicity], and Johnson et al. (2003) [fetal heart malformations] as the critical studies and effects for non-cancer dose-response assessment;
    h. The selection of the draft RfC and RfD on the basis of multiple critical effects for which candidate reference values are at the low end of those for the full range of candidate critical effects, rather than on the basis of the single most sensitive critical effect.

5. Is the dose-response assessment for cancer effects clearly and transparently described, and adequately justified to support EPA's draft inhalation and oral unit risks? Are there changes in the cancer dose-response analyses that should be considered that would make a significant impact on the accuracy, objectivity, transparency, or utility of EPA's quantitative conclusions? Specific issues to address include:
    a. Use of Charbotel et al. (2006) case-control study to estimate unit risks for renal cell carcinoma;

b. Use of meta-analysis results and Raaschou-Nielsen et al. (2006) to adjust renal cell carcinoma unit risks to account for the added risk of tumors at other sites for which there is substantial evidence of carcinogenic hazard;
c. Use of rodent bioassays to estimate human unit risks for cancer;
d. Selection of PBPK-based dose metrics for inter-species, intra-species, and route-to-route extrapolation based on internal dose;
e. Consistency of estimates based on human and rodent data;
f. The preference for estimates based on human epidemiologic studies;
g. Characterization of uncertainty and variability;
h. Application of the Age-Dependent Adjustment Factor for TCE-induced kidney cancer risks due to the conclusion that the weight of evidence supports a mutagenic mode of action for that endpoint.

6. Please identify any additional studies that would make a significant impact on the conclusions of the Toxicological Review, and should therefore be considered in the assessment of the noncancer and cancer health effects of TCE.

7. Please discuss research likely to substantially increase confidence in the database for *future* assessments of TCE.