NCEA's Proposed Charge to External Peer Reviewers for the IRIS Toxicological Review of Trichloroethylene (TCE)
October 2009

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).

In 2000, a monograph comprising 16 articles on the "State-of-the-Science" on TCE health risks, co-sponsored by EPA, other federal agencies, and the Halogenated Solvents Industry Alliance, 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 at which recently published research was presented by a number of scientists.[4] Due to continuing scientific issues as well as emerging significant new science, EPA cosponsored with the Department of Defense, Department of Energy, and the National Aeronautics and Space Administration 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 human health risk assessment is based on a comprehensive review of the available scientific literature on the human health effects of TCE, consideration of the input and advice from all the above sources, and adherence to the general guidelines for risk assessment set 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

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

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 evidence, and presents a quantitative risk assessment for TCE health effects, including the derivations of a chronic inhalation Reference Concentration (RfC) and chronic oral Reference Dose (RfD) 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, and focus any recommendations on improving the accuracy, objectivity, transparency, and utility of EPA's current analyses and conclusions.

PBPK Modeling

1. Is EPA's updated PBPK model for TCE and its metabolites (also reported in Evans et al., 2009, and Chiu et al., 2009) clearly and transparently described and technically and scientifically adequate for supporting EPA's hazard characterization and dose-response assessment? Specifically, please address the PBPK model structure; Bayesian statistical approach; parameter calibration; model predictions of the available in vivo data; and characterization of PBPK model dose metric predictions, including those for the GSH conjugation pathway.

Meta-analysis of cancer epidemiology

2. NRC (2006) recommended that EPA develop updated meta-analyses of the epidemiologic data on TCE exposure and cancer, and provided advice as to how EPA should conduct such analyses. Is EPA's updated meta-analysis of the epidemiologic data on TCE exposure and kidney cancer, lymphoma, and liver cancer clearly and transparently described and technically and scientifically adequate for supporting EPA's hazard characterization and dose-response assessment? Specifically, please address the standards of epidemiologic study design and analysis as they were applied to select studies for inclusion in the meta-analysis; the rationales for study relative risk estimate selections; the meta-analysis methods; and the characterization of the conclusions of the meta-analyses.
   Note: The scope of this charge question only includes the meta-analysis methods and results and not the overall weight of evidence for TCE carcinogenicity, which is addressed as part of a subsequent charge question.

Hazard Assessment

3. Does EPA's hazard assessment of non-cancer human health effects of TCE logically, accurately, clearly, and objectively represent and synthesize the available scientific evidence to support its conclusions that TCE poses a potential human health hazard for

non-cancer toxicity to the central nervous system; the kidney; the liver; the immune system; the male reproductive system; and the developing fetus, including the role of TCE in inducing fetal cardiac defects?

4. Using the approach outlined in the U.S. EPA Cancer Guidelines (U.S. EPA, 2005a), does EPA's hazard assessment of carcinogenicity logically, accurately, clearly, and objectively represent and synthesize the available scientific evidence to support its conclusions that TCE is carcinogenic to humans by all routes of exposure? Specifically, please address the epidemiologic evidence for associations between TCE and kidney cancer, lymphoma, and liver and biliary tract cancer; the extent to which the results of the meta-analyses contribute to the overall weight of evidence for TCE carcinogenicity; the laboratory animal data for rat kidney tumors, mouse liver tumors, and lymphatic cancers in rats and mice; and the toxicokinetic and other data supporting TCE carcinogenicity by all routes of exposure.

5. Does EPA's hazard assessment logically, accurately, clearly, and objectively represent and synthesize the available scientific evidence to support its conclusions regarding the role of metabolism in TCE carcinogenicity and non-cancer effects? Specifically, please address EPA's conclusions that the liver effects induced by TCE are predominantly mediated by oxidative metabolism, but not adequately accounted for by the metabolite trichloroacetic acid (TCA) alone and that the kidney effects induced by TCE are predominantly mediated by metabolites formed from the GSH-conjugation pathway.

6. Using the approach outlined in the U.S. EPA Cancer Guidelines (U.S. EPA, 2005a), does EPA's hazard assessment logically, accurately, clearly, and objectively represent and synthesize the available scientific evidence to support its conclusions regarding the mode(s) of action [MOA(s)] of TCE carcinogenicity and non-cancer effects? Specifically, please address the conclusions that the weight of evidence supports a mutagenic MOA for TCE-induced kidney tumors; that a MOA for TCE-induced kidney tumors involving cytotoxicity and compensatory cell proliferation, possibly in combination with a mutagenic MOA, is inadequately supported by available data; that there is inadequate support for PPARα agonism and its sequellae being key events in TCE-induced liver carcinogenesis; that there are inadequate data to specify the key events and MOAs involved in other TCE-induced cancer and non-cancer effects; and that the available data are inadequate to conclude that any of the TCE-induced cancer and non-cancer effects in rodents are not relevant to humans

7. Does EPA's hazard assessment logically, accurately, clearly, and objectively represent and synthesize the available scientific evidence to support its conclusions that the factors that could modulate susceptibility to TCE carcinogenicity and non-cancer effects include genetics, lifestage, background and co-exposures, and pre-existing conditions, but that only toxicokinetic variability in adults can be quantified given the available data?

Dose-Response Assessment

8. EPA's dose-response assessment includes the development of a chronic inhalation Reference Concentration (RfC) and chronic oral Reference Dose (RfD) for non-cancer effects. Please address the following methods and results from EPA's non-cancer dose-response assessment in terms of the extent to which they are clearly and transparently described and technically/scientifically adequate to support EPA's draft RfC and RfD:
    a. The screening, evaluation, and selection of candidate critical studies and effects;
    b. The points of departure, including those derived from benchmark dose modeling (e.g., selection of dose-response models, benchmark response levels);
    c. The selected 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. The selected uncertainty factors;
    e. The equivalent doses and concentrations for sensitive humans developed from PBPK modeling to replace standard uncertainty factors for inter- and intra-species toxicokinetics, including selection of the 99th percentile for overall uncertainty and variability to represent the toxicokinetically-sensitive individual;
    f. The qualitative and quantitative 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 in a narrow range at the low end of the full range of candidate critical effects, rather than on the basis of the single most sensitive critical effect.

9. In accordance with the approach outlined in the U.S. EPA Cancer Guidelines and Supplemental Guidance (U.S. EPA, 2005a; U.S. EPA, 2005b), EPA's dose-response assessment includes the development of an inhalation unit risk and oral unit risk for the carcinogenic potency of TCE. Please address the following methods, results, and conclusions from EPA's cancer dose-response assessment in terms of the extent to which they are clearly and transparently described and technically/scientifically adequate to support EPA's draft inhalation and oral unit risks:
    a. the estimation of unit risks for renal cell carcinoma from the Charbotel et al. (2006) case-control study;
    b. the adjustments of renal cell carcinoma unit risks to account for the added risk of other cancers using the meta-analysis results and Raaschou-Nielsen et al. (2006);
    c. the estimation of human unit risks from rodent bioassays;
    d. in accordance with the approach in the U.S. EPA Cancer Guidelines (U.S. EPA, 2005a) and the conclusions as to MOA (above), the use of linear extrapolation from the point of departure (POD) for the cancer dose-response assessment of TCE;

e. the applications of PBPK modeling, including the selection of dose metrics and the use of PBPK model predictions for inter-species, intra-species, and route-to-route extrapolation based on internal dose, and their preference over default approaches based on applied dose;
f. the qualitative and quantitative characterization of uncertainty and variability;
g. the conclusion that the unit risk estimates for TCE based on human epidemiologic data and those based on rodent bioassay data are consistent overall; and,
h. the preference for the unit risk estimates for TCE based on human epidemiologic data over those based on rodent bioassay data.

10. Based on the conclusions that the weight of evidence supports a mutagenic MOA for TCE-induced kidney cancer and that the MOAs for TCE-induced liver cancer and lymphomas are not known, the Age-Dependent Adjustment Factors (ADAFs) are only applied to the kidney cancer component of the unit risk estimates. Please address the extent to which the recommended approach to applying the ADAFs in this situation is clearly, transparently, and accurately described.

Additional key studies

11. 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.

Research Needs

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