SDMS DocID 2095140

United States
Environmental
Protection Agency

EPA Science Advisory
Board (1400A)
Washington, DC

EPA-SAB-EHC-03-002
December 2002
www.epa.gov/sab

EPA

# Review of Draft Trichloroethylene Health Risk Assessment: Synthesis and Characterization: An EPA Science Advisory Board Report

## A REVIEW BY THE TCE REVIEW PANEL OF THE ENVIRONMENTAL HEALTH COMMITTEE OF THE US EPA SCIENCE ADVISORY BOARD (SAB)

AR100165

**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**
**WASHINGTON, D.C. 20460**

December 2, 2002

**OFFICE OF THE ADMINISTRATOR**
**SCIENCE ADVISORY BOARD**

EPA-SAB-EHC-03-002

The Honorable Christine Todd Whitman
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Review of Draft Trichloroethylene Health Risk Assessment: Synthesis and Characterization: An EPA Science Advisory Board Report

Dear Governor Whitman:

A Panel (Trichloroethylene Health Risk Assessment: Synthesis and Characterization Review Panel) of the U.S. EPA Science Advisory Board's Environmental Health Committee met on June 18-19, 2002 to review the Agency's draft human health assessment, "Trichloroethylene Health Risk Assessment: Synthesis and Characterization."

The Board advises the Agency to move ahead to revise and complete this important assessment. The assessment addresses a chemical, trichloroethylene (TCE), significant for being a nearly ubiquitous environmental contaminant in both air and water, being a common contaminant at Superfund sites, and because it is "listed" in many Federal statutes and regulations. The draft assessment is also important because it sets new precedents for risk assessment at EPA. We believe the draft assessment is a good starting point for completing the risk assessment of TCE. The Panel commends the Agency for its effort and advises it to proceed to revise and finalize the draft assessment as quickly as it can address the advice provided in this report.

The Board commends the Agency for its groundbreaking work in this draft assessment in several important new areas in risk assessment: a) risk to children and other susceptible populations; b) cumulative risk; c) examination of multiple kinds of evidence including evidence about physiological and molecular modes of action; d) the assessment of the health risks associated with the many metabolites of TCE; e) the use of biologically-based modeling; f) the explicit recognition and acknowledgment of uncertainties in the risk analysis; and g) the consideration of multiple data sets from animal and human studies to derive cancer slope factors.

Although the Board welcomes this effort, it also cautions the Agency that the new areas explored involve considerable uncertainty. Progress in reducing these uncertainties will be an evolutionary process that will necessitate advancements in scientific research and analysis. The Board also notes that there is a need for Agency-wide guidance in many of the areas explored in the draft assessment. The Agency should develop consistent policies across program areas on protection of children and other vulnerable populations, cumulative risk, and aggregate risk

Because the draft assessment breaks ground in several areas and sets important precedents, there is a need to strengthen the rigor of the discussion in the revised assessment so that the basis for all derived values is transparent and clearly supported by the available data. The Board notes that public comments have raised valid concerns the Agency should carefully address. The Panel urges the Agency to review and address the public comments it received on

the review draft, especially those from experts who had conducted research related to the assessment of TCE's health risks and whose reviews had been published in a supplemental issue of Environmental Health Perspectives (Volume 108, Supplement 2, May 2000).

The Board notes five key substantive areas for the Agency to address: a) the need to strengthen and expand the use of epidemiology data to update the uncertainty analysis, to incorporate new studies, and to focus on first tier studies and case-control studies that specifically address TCE exposure; b) the need to develop a more formal method for selecting and weighing evidence and communicating those decisions, when information comes from multiple lines of evidence; c) the need for a more detailed explanation for the Agency's treating cancer mode of action in a linear way, even as the Board notes that the Agency had provided clear criteria for the choice of a linear approach; d) the need to explain the derivation of the RfD and RfC study-by-study, endpoint-by-endpoint; e) the need to quantify and provide more explicit justification for the background exposures to be included in uncertainty factors and incorporated in the TCE assessment; and f) the need to be explicit about the assumptions underlying its analyses.

In addition, to strengthen and provide confidence in the Agency's assessment, the Board has identified several needs. There is the need for a summary paragraph in each section describing the Agency position/conclusion and a clear description in each section of the scientific basis for those choices and other alternatives considered. The Agency should develop a new children's chapter to discuss the pharmacokinetic, pharmacodynamic, and risk assessment conclusions in a comprehensive unified chapter focused on children's health. The new children's chapter should offer a model for other draft assessments to follow and would integrate information about specific aspects of risks to children's health as discussed in the other sections of the assessment. And finally, and most importantly, there is a need to enable others to reproduce the calculations and models on which the assessment's conclusions are based. Therefore, we strongly advise the Agency to reference original papers on key issues, not only review articles, and to provide access to data, documentation, and results of intermediate calculations from which the Agency's results can be recreated.

In closing, the Board greatly appreciates the efforts of the Agency's staff developing this groundbreaking assessment. We look forward to your response to this report.

Sincerely,

***/Signed/***

Dr. William Glaze, Chair
EPA Science Advisory Board

***/Signed/***

Dr. Henry Anderson, Chair
Environmental health Committee, and
Trichloroethylene Health Risk Assessment: Synthesis and Characterization Review Panel
EPA Science Advisory Board



AR100167

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AR100168

# ABSTRACT

A Panel of the U.S. EPA Science Advisory Board's Environmental Health Committee reviewed the Agency's draft human health assessment, "Trichloroethylene Health Risk Assessment: Synthesis and Characterization." It responded to Agency charge questions that touched on how the document addressed several important new areas in risk assessment: a) risk to children and other susceptible populations; b) cumulative risk; c) examination of multiple kinds of evidence including evidence about physiological and molecular modes of action; d) the assessment of the health risks associated with the many metabolites of TCE; e) the use of biologically-based modeling; f) the explicit recognition and acknowledgment of uncertainties in the risk analysis; and g) the consideration of multiple data sets from animal and human studies to derive cancer slope factors.

The Board commends the Agency for its groundbreaking work in this draft and advises the Agency to move ahead to revise and complete this important assessment.

The Board also cautions the Agency that the new areas explored involve considerable uncertainty. Progress in reducing these uncertainties will be an evolutionary process that will necessitate advancements in scientific research and analysis. The Board also notes that there is a need for Agency-wide guidance in many of the areas explored in the draft assessment. The Agency should develop consistent policies across program areas on protection of children and other vulnerable populations, cumulative risk, and aggregate risk. Because the draft assessment breaks ground in several areas and sets important precedents, there is also a need to strengthen the rigor of the discussion in the revised assessment so that the basis for all derived values is transparent and clearly supported by the available data. The Board identifies five key substantive areas for the Agency to address and also ways to revise the document to strengthen and provide confidence in the Agency's assessment.

**Keywords:** TCE, Risk Assessment, Human Health, Children's Health, Pharmacokinetic Modeling



AR100169

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**Science Advisory Board**
**Environmental Health Committee**
**Trichloroethylene Health Risk Assessment:**
**Synthesis and Characterization Review Panel***

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AR100170

# TABLE OF CONTENTS

1. EXECUTIVE SUMMARY OF RESPONSES TO CHARGE QUESTIONS . . . . . 1

2. INTRODUCTION . . . . . 4
   2.1. Background . . . . . 4
   2.2. Process for Developing this Report . . . . . 5

3. CHARGE QUESTION 1 . . . . . 6
   3.1. Agency Charge Question and Suggested Areas for Inquiry . . . . . 6
   3.2. Panel Response . . . . . 6

4. CHARGE QUESTION 2 . . . . . 10
   4.1. Agency Charge Question and Suggested Areas for Inquiry . . . . . 10
   4.2. Panel Response . . . . . 10
      4.2.1. Cancer Classification for TCE . . . . . 10
      4.2.2. Human Epidemiological Studies . . . . . 11
      4.2.3. Animal Toxicology . . . . . 13

5. CHARGE QUESTION 3 . . . . . 16
   5.1. Agency Charge Question and Suggested Areas for Inquiry . . . . . 16
   5.2. Panel Response . . . . . 16

6. CHARGE QUESTION 4 . . . . . 18
   6.1. Agency Charge Question and Suggested Areas for Inquiry . . . . . 18
   6.2. Panel Response . . . . . 18
      6.2.1. Multiple Critical Effects: Does the draft assessment adequately characterize the data at each site of toxicity and focus on an appropriate subset of critical effects? . . . . . 18
      6.2.2. Modes of Action of TCE Toxicity . . . . . 20
      6.2.3. Uncertainty Factors - Areas of Agreement and Differences Within the Panel . . . . . 20

7. CHARGE QUESTION 5 . . . . . 25
   7.1. Agency Charge Question and Suggested Areas for Inquiry . . . . . 25
      7.2.1. Panel Response . . . . . 25
         7.2.1.1 Clarification of the Cancer Slope Factors . . . . . 25
         7.2.1.2 Suitability and Use of the Cancer Slope Factors . . . . . 26
         7.2.1.3 Improved Mediation of the Cancer Slope Factors . . . . . 27
      7.2.2. Further Studies to Be Included . . . . . 28
      7.2.3. Linear or Nonlinear Approach . . . . . 28
      7.2.4. Sensitive Populations . . . . . 29
      7.2.5. For Further Consideration . . . . . 29

8. CHARGE QUESTION 6 . . . . . 30
   8.1. Agency Charge Question and Suggested Areas for Inquiry . . . . . 30
   8.2. Panel Response . . . . . 30
      8.2.1. Modeling . . . . . 31
      8.2.2. Uncertainty Analysis . . . . . 32
      8.2.3. Data Availability . . . . . 33
      8.2.4. Markov-Chain Monte Carlo (MCMC) . . . . . 34



AR100171

9. CHARGE QUESTION 7 . . . . . 35
9.1. Agency Charge Question and Suggested Areas for Inquiry . . . . . 35
9.2. Panel Response . . . . . 35

10. CHARGE QUESTION 8 . . . . . 38
10.1. Agency Charge Question and Suggested Areas for Inquiry . . . . . 38
10.2. Panel Response . . . . . 38

11. CHARGE QUESTION 9 . . . . . 39
11.1. Agency Charge Question and Suggested Areas for Inquiry . . . . . 39
11.2. Panel Response . . . . . 39
11.2.1. Major Summary Consensus Points of the Panel . . . . . 39
11.2.2 Background to the Panel's Conclusions . . . . . 40
11.2.3. How the Draft Assessment Can Be Improved . . . . . 44

REFERENCES . . . . . R-1

APPENDIX A
SPECIFIC PANEL COMMENTS ON THE AGENCY'S ASSESSMENT OF NONCANCER ENDPOINTS . . . . . A-1
1. Specific Comments on Hazard Characterization for Noncancer Endpoints . . . . . A-1
1.1. Liver Effects . . . . . A-1
1.2. Kidney Effects . . . . . A-1
1.3. Developmental Effects . . . . . A-2
1.4. Neurotoxicity Effects . . . . . A-3
1.5. Endocrine System Effects and Reproductive Toxicity Effects . . . . . A-3
2. Specific Comments on Uncertainty Factors for NonCancer Endpoints . . . . . A-4
2.1. Human Variation . . . . . A-4
2.2. Animal-to-Human Uncertainty . . . . . A-5
2.3. Subchronic-to-Chronic Uncertainty . . . . . A-5
2.4. LOAEL-to-NOAEL Uncertainty . . . . . A-6
2.5. Other Factors . . . . . A-9

APPENDIX B
RECENT RESEARCH ON GENERAL PHARMACOKINETIC DIFFERENCES BETWEEN CHILDREN OF VARIOUS AGES AND ADULTS . . . . . B-1

APPENDIX C
Biosketches of Members of the US EPA Science Advisory Board (SAB) Trichloroethylene Health Risk Assessment: Synthesis and Characterization Review Panel (TCE Review Panel). . . . . C-1



AR100172

# 1. EXECUTIVE SUMMARY OF RESPONSES TO CHARGE QUESTIONS

a) Charge Question 1: Does the assessment adequately discuss the likelihood that trichloroethylene (TCE) acts through multiple metabolites and multiple modes of action?

Panel's Response: EPA should be commended for its efforts to date to evaluate a wide variety of hypotheses for the carcinogenic and other toxic effects of TCE. The draft assessment could be enhanced by including additional selective quantitative analysis and further evaluation of dose-response relationships, especially relationships that may clarify the role of different metabolites in the toxicity of TCE at human exposure levels. Panel members offered several examples of quantitative analyses that the Agency could use to improve the document.

b) Charge Question 2: Is the cancer weight-of-evidence characterization adequately supported?

Panel's Response: The Panel commends EPA for compiling an extensive array of scientific literature that included over 80 epidemiological studies and hundreds of toxicological and mechanistic studies and for characterizing the evidence relatively clearly and cohesively. The Panel feels that the Agency's overall qualitative cancer risk characterization was reasonable based on: a) significant experimental evidence showing tumors at multiple sites in two species (rats and mice); b) epidemiologic evidence in humans showing associations between TCE exposure and several cancers including at several of the same sites seen in animal bioassays; and c) mechanistic data indicating relevance of experimental findings to humans. There was a suggestion that EPA clarify more explicitly for the public what is meant by a "weight-of-evidence characterization."

The Panel also advises the Agency to improve the characterization of the cancer weight-of-evidence by evaluating human and animal studies more rigorously, explicitly using Agency criteria for evaluating those studies. On a related issue, several panel members noted that the assessment could be strengthened if the Agency emphasized and integrated information about dose-response and if it presented a coherent analysis of quantitative information available on the mode-of-action of metabolites. The Panel also advises the Agency to provide a more thorough discussion and critical evaluation of the conflicting human epidemiological evidence for kidney tumors.

The Panel suggests that it is important to provide both upper confidence limit estimates and the mean "expected value" estimate when developing risk ranges to give users confidence intervals. It notes that it will also be important for the Agency to provide risk management guidance that might indicate when it is most appropriate to use mean values, or when to use high end values with confidence intervals

c) Charge Question 3: A new feature of the cancer database is molecular information on the von Hippel-Lindau tumor suppressor gene. Is this information adequately discussed and are the conclusions appropriate.

Panel's Response: The consensus of the panel is that the discussion in the draft assessment is generally appropriate. The panel generally agrees that EPA is wise not to regard the evidence as entirely conclusive pending independent confirmation. The discussion in the draft assessment might be improved by including some additional comparative observations from kidney cancers not in the TCE exposed workers.



AR100173

d) Charge Question 4: Does the assessment adequately discuss the use of multiple critical effects in developing an oral reference dose (RfD) and inhalation reference concentration (RfC) for effects other than cancer? Are the uncertainty factors well discussed and well supported?

Panel's Response: The Panel commends the Agency for consideration of multiple noncancer endpoints in both the general discussion and in the derivation of the RfD and RfC. TCE clearly has important hepatotoxic, nephrotoxic, neurotoxic, immunologic, developmental and reproductive effects that should be considered in the derivation of the RfD and RfC. The use of multiple critical effects increases one's confidence that the point of departure dose is at the low end of doses at which adverse effects can be observed.

Some panel members suggested that the characterization of the data at each site of toxicity could be strengthened considerably. The Panel recognizes that a lengthy dissertation of each study cited by EPA would be counterproductive. However, in the opinion of some panelists, the current discussion lacks the type of critical analysis and discussion of the weight-of-evidence that is necessary to understand the Agency's rationale for selection of endpoints, level of concern, dose-response extrapolation, effect of time-duration on key endpoints, and application of uncertainty factors. Other panel members thought the discussion of non-cancer effects and discussions surrounding the development of the RfD and RfC were quite good and that with relatively limited additional clarification the non-cancer section of the draft assessment would be complete.

e) Charge Question 5: Does the assessment adequately discuss the derivation of a range of estimates for the cancer risk? Are there any studies that should/should not have been included?

Panel's Response: The Panel commends EPA for the derivation of a set of cancer risk estimates or cancer slope factors (CSF) for TCE in the draft assessment. The presentation of a range of estimates is a step forward for EPA towards a more explicit and more quantitative representation of the substantial uncertainties in estimates of cancer risks.

The Panel identifies a key study (Hansen et. al., 2001) that should be included in the revision of the draft assessment. The Panel advises that, where epidemiological studies are the basis of risk estimates, EPA should select the broadest possible array of studies for each endpoint taking into consideration study design, availability of exposure estimates, and the goal of protecting health. The Panel commends the Agency for providing sections on sensitive populations and cumulative risks and added several suggestions for strengthening quantitative aspects of the risk assessment methodology that are important for the refinement of the risk assessment of TCE.

f) Charge Question 6: Please comment on the use of calibrated models and uncertainty analysis to address the question of pharmacokinetic model uncertainty.

Panel's Response: The Panel commends the Agency's inclusion of physiologically-based pharmacokinetic models and its explicit recognition of model uncertainty in the draft assessment. It advises the Agency to explain the modeling methods more clearly, and to make the models, data, and assumptions used available, so that the Agency's results can be reproduced. The Panel calls on the Agency to compare the two calibrated models used and to show how the models and analyses compare and relate to one another. The Panel advises the Agency to highlight the impact of the uncertainty analysis on the dose estimates of the different models and on the dose-response analysis and to explain the differences between the models and the ranges of uncertainty.

g) Charge Question 7: Is it appropriate to consider background exposures and other characteristics of an exposed population as modulating the risk of TCE exposure in that population?

Panel's Response: The Panel is pleased that the Agency has taken the first steps of including the issue of cumulative risk in a health risk assessment. Although there was agreement that background exposures to TCE and/or metabolites is a very important issue, there was disagreement about whether the RfD, and the uncertainty factor used to derive it, should be the method by which this background exposure is addressed. The Panel agrees, however, that regardless of EPA's final policy decision on whether or not to include an additional uncertainty factor in the RfD for background exposure, more attention and detail is needed to provide a rationale for the Agency's use of such an uncertainty factor.

h) Charge Question 8: Do the data support identifying risk factors that may be associated with increased risks from TCE exposure? Are there any risk factors that should/should not have been included?

Panel's Response: The Panel finds that the data support identifying numerous risk factors that may be associated with increased risks to susceptible subpopulations from TCE exposure. The EPA draft assessment has done a good job identifying the general areas of concern related to prenatal, reproductive and developmental risks associated with TCE exposure, especially given the level of information known to date. The Panel agrees with the draft risk assessment's identification of multiple background exposures to ethanol, TCE, and its metabolites, and other chemical solvent mixtures as factors that may be associated with increased risks.

i) Charge Question 9: Do the data support the possibility that TCE can affect children and adults differently? Should this be reflected in the quantitative assessment?

Panel's Response: The Panel reached consensus on the following conclusions related to this charge question: a) the data presented suggest that TCE can affect children differently than adults, although there is a very limited database of TCE in children due to lack of directly applicable studies; b) the draft does not explicitly discuss whether or not the uncertainty factors adequately address risk to children or attempt to develop toxicity values that take children into consideration; c) the Panel advises the Agency to develop a stand-alone comprehensive children's chapter that discusses all the children's issues, including exposure, susceptibility during pregnancy, pharmacokinetics, and pharmacodynamics, in addition to discussing developmental animal and children data in every section; and d) the Panel advises the Agency to support statements about differences between children and adults with a quantitative discussion, whenever possible. Although the Panel differs on the question of whether the Agency should add a quantitative uncertainty factor to protect children above the composite uncertainty factor already in the draft assessment, it did advise the Agency to address this issue explicitly and to clarify how such a factor would relate to other uncertainty factors used.

# 2. INTRODUCTION

## 2.1. Background

The purpose of this report is to provide advice to the Agency in developing a final health risk assessment for TCE. The SAB formed the Trichloroethylene Health Risk Assessment: Synthesis and Characterization Review Panel to review a draft assessment dated August 2001 that EPA's Office of Research and Development (ORD) provided for external public comment on September 19, 2001.[1] TCE is a major contaminant of concern in EPA's air, water, and waste programs. EPA's regulatory program and regional offices have identified TCE as among the highest priorities for a new assessment.

The Agency has noted, and the Panel acknowledges, that the draft assessment submitted for review was shaped by several new developments in risk assessment. The practice of risk assessment has been evolving from a focus on a single toxic effect of one pollutant in one environmental medium toward integrated assessments covering multiple effects and multiple media and incorporating information about mode of action, uncertainty, human variation, and cumulative effects of multiple pollutants in different media. This evolution has responded to recommendations of the National Research Council, whose recommendations have been embraced in EPA's proposed cancer guidelines.

The TCE draft assessment breaks new ground in addressing the new dimensions of risk assessment that EPA and others have advocated. The draft assessment discusses the possibility that children, infants, and the developing fetus may differ from adults with respect to susceptibility to TCE's toxic effects. The assessment also addresses cumulative risks by discussing the implications of other chlorinated solvents and agents that have metabolic pathways, potential modes of action, and toxic effects similar to TCE. The assessment implements principles of the proposed cancer guidelines by emphasizing characterization discussions, and by using information on mode-of-action and information on susceptible populations to derive cancer slope factors and RfD and RfC values

The issues surrounding TCE are quite complex, with extensive information in some areas and relatively little information in others. EPA's ORD initiated development of 16 peer-reviewed state-of-the-science papers that were published in a special supplementary issue of the journal Environmental Health Perspectives (May 2000). The Agency acknowledged that it drew on those papers, plus some other key references, as scientific support for the draft assessment.

In the fall of 2001, EPA asked the SAB to convene a Panel to address the following draft charge questions:

a) Does the assessment adequately discuss the likelihood that trichloroethylene (TCE) acts through multiple metabolites and multiple modes of action?

b) Is the cancer weight-of-evidence characterization adequately supported?

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[1] U.S. Environmental Protection Agency, Trichloroethylene Health Risk Assessment: Synthesis and Characterization, External Review Draft, August 2001, EPA/600/P-01/002A



AR100176

c) A new feature of the cancer database is molecular information on the von Hippel-Lindau tumor suppressor gene. Is this information adequately discussed and are the conclusions appropriate?

d) Does the assessment adequately discuss the use of multiple critical effects in developing an oral reference dose (RfD) and inhalation reference concentration (RfC) for effects other than cancer? Are the uncertainty factors well discussed and well supported?

e) Does the assessment adequately discuss the derivation of a range of estimates for the cancer risk? Are there any studies that should/should not have been included?

f) Please comment on the use of calibrated models and uncertainty analysis to address the question of pharmacokinetic model uncertainty.

g) Is it appropriate to consider background exposures and other characteristics of an exposed population as modulating the risk of TCE exposure in that population?

h) Do the data support identifying risk factors that may be associated with increased risks from TCE exposure? Are there any risk factors that should/should not have been included?

i) Do the data support the possibility that TCE can affect children and adults differently? Should this be reflected in the quantitative assessment?

### 2.2. Process for Developing this Report

The SAB formed a special panel to address the Agency's charge questions. It was composed of members of the SAB's Environmental Health Committee, augmented to provide additional expertise needed to address the charge and to provide breadth of viewpoints on issues key to the review. Panel members were added to provide expertise in the following areas: TCE epidemiology; pharmacokinetic modeling; cancer toxicity biostatistics, and modeling; modes of action at the molecular level; modes of action at the physiological level; differing perspectives on how the toxicology database of information on TCE can be understood; and risk assessment expertise. Biosketches of panel members can be found in Appendix C.

The Panel reviewed the Agency's draft assessment, along with supplementary background information that included: a) Environmental Health Perspectives (May 2000); b) Summary of Public Comments for EPA's Science Advisory Board; c) Log of public comments for "Trichloroethylene (TCE) Health Risk Assessment Synthesis and Characterization;" and d) over 800 pages of public comments.

The Panel held a public planning teleconference on June 5, 2002. At that meeting it considered "areas of inquiry" suggested by the Agency to help guide the Panel's discussion of the nine charge questions. These "areas of inquiry," suggested by the Agency, are included in the different sections of the Panel's report below.

The Panel held a face-to-face public meeting in Washington D.C. on June 18-19, 2002, and a public teleconference to discuss this report in draft form on July 18, 2002.



AR100177

## 3. CHARGE QUESTION 1

### 3.1. Agency Charge Question and Suggested Areas for Inquiry

Charge Question: Does the assessment adequately discuss the likelihood that trichloroethylene (TCE) acts through multiple metabolites and multiple modes of action?

Suggested Areas for Inquiry: A prominent issue is the role of the metabolite DCA. One view is that DCA has little or nothing to do with TCE's toxicity; another view is that more than one metabolite (both TCA and DCA) could be responsible for TCE's effects in the liver. The draft assessment discusses the evidence supporting both positions, as well as potential modes of action and metabolites involved at other sites of toxicity. Does the draft assessment adequately consider and characterize such information?

### 3.2. Panel Response

EPA should be commended for its efforts to date to evaluate a wide variety of hypotheses for the carcinogenic and other toxic effects of TCE and its different metabolites. The draft assessment could be enhanced by considering additional selective quantitative analysis and further evaluation of dose-response relationships. Panel members offered several examples of quantitative analyses that the Agency could use to improve the document.

a) The discussion of the potential roles of TCA vs. DCA in the causation of liver cancers can be usefully informed by comparing the observed liver cancers in existing animal bioassays with those that would be predicted based on:

> 1) calculations of the potency of these metabolites when administered separately in similar animal model systems, and
>
> 2) pharmacokinetic modeling estimates of how much of each metabolite would be produced from TCE under the bioassay conditions.

The Panel advises the Agency to base potency estimates of the metabolites resulting from direct exposure, versus exposure from TCE metabolism on time-dependent liver dosimetry.

Some analysis along these lines seems to be contained in the state-of-the-science paper by Chen (2000). In the paper by Bull et al. (2000), there is a discussion concerning the effective level of TCE metabolites in blood following administration of TCE, TCA, and DCA that causes liver tumors. It should be recognized that estimations of blood metabolite levels would not be adequate for trans-species extrapolations, because of possible differences in the partition coefficients in rodents versus humans.

Critical review of this information could be incorporated into Section 3.5 of the Agency's draft assessment to help evaluate the likely contributions of the different metabolites to the liver tumor observations.

b) TCA is metabolized to DCA yet the liver tumors induced by DCA display different characteristics compared to the tumors induced by TCA (section 3.5.1.2). Was a comparison of these tumor characteristics induced by TCA and DCA ever made to similar tumors produced by TCE? Again, a quantitative discussion of the levels of these metabolites present following administration of the metabolite or the parent TCE would be useful.



AR100178

c) Another example of a quantitative analysis suggested by a panel member relates to the peroxisome proliferator hypothesis for the mode of action of TCE and/or its metabolites. For this hypothesis for the mode of action, there should be a reasonably good quantitative correlation between the peroxisome proliferation potency and the apparent carcinogenic potency of TCE and possibly its relevant metabolites across species, genders, etc. From the Bull (2000) report in the state-of -the science papers that TCE induces peroxisome proliferation in rats but not liver tumors, and some other comments there, it appears that the correlation may not be very good. If so, a quantitative comparative analysis will reveal that.

In the absence of such a demonstrated correlation between the potencies for causing peroxisome proliferation and the potencies for causing liver cancer, several members of the Panel do not completely understand the relatively favorable attention given to this possibility in the draft assessment. The Panel believes the potential mode of action discussion should include this hypothesis in the review. However some panel members suggested that EPA should consider giving it somewhat less weight than the possibility that increases in cell replication rates interact with some amount of classical mutagenic/clastogenic activity by highly reactive intermediates such as the TCE-epoxide or metabolites of the metabolites TCA and DCA (see suggestion below that additional quantitative analysis of genotoxic hypotheses be included to the extent possible based on available data). One panelist suggested that the open question of the possible contribution of the release of free TCE-epoxide and resulting DNA reactions be at least mentioned in the revised draft assessment. It also should be noted that the mechanisms by which TCE metabolites affect cell cycling have not been sufficiently worked out so as to provide a clear indication on how these changes in relation to metabolite dosimetry and as a function of age relate to the probability of liver tumor development.

d) In section 3.5.1.2, the cell-signaling mode of action for TCA and DCA is discussed. The only paper that is cited that supports this mode of action is by Bull (2000). Are there other studies in which this potential mode of action is supported? If so, they should be included. The responses observed for TCA and DCA are not compared specifically to what occurs following doses of TCE that cause observed liver tumors. Are these data available? If not, the Panel advises EPA to present the doses of TCA and DCA administered to cause these responses along with a prediction [utilizing physiologically-based pharmacokinetic (PBPK) models] of the dosimetry of these metabolites in the liver following administered dose of the metabolite or TCE.

e) A more quantitative discussion of the genotoxic data relative to cytotoxicity and tumor formation is especially important in clarifying the genotoxic contributions to carcinogenic action and in understanding the shape of the dose-response curve at human exposure levels. The Agency's characterization of TCE and its major metabolites as "weak" mutagens/clastogens in various test systems implies that the observed rather low potency for carcinogenic activity by TCE is somehow not consistent with a primary genetic mode of action because TCE and its metabolites do not have what might be called "strong" potency for mutagenic endpoints. The use of terms such as "weak" and "strong" in this context is vague and open to misinterpretaton. If arguments of this sort are to be used by the Agency, the Panel advises EPA to base those arguments on quantitative analysis of the correlation between mutagenic potency in specific test systems used for TCE and its metabolites and carcinogenic potencies for chemicals (perhaps related chemicals) as conventionally determined by EPA procedures. Readers can then assess the usefulness of such correlations for supporting inferences about the mutagenic/clastogenic potency of major TCE metabolites and the potential for a genetic mode of action. The general impression of some panel members is that such correlations, while present, are imprecise. They will not support a strong inference that relatively low mutagenic/clastogenic potency by major TCE metabolites is inconsistent with a genetic mode of action for the relatively low carcinogenic

potency of TCE, compared with other related small-molecular-weight organic chemical carcinogens.

An important issue concerned the mechanism for liver cancer. The Panel advises the Agency to explore hypotheses for both non-genotoxic and genotoxic mechanisms for liver cancer, considering effects at different dose levels. The Panel advises the Agency to consider the information and hypotheses provided in the state-of-the-science papers (e.g., Bull, 2000) and other relevant literature.

Some other comments by panel members suggested various types of summaries to strengthen the draft assessment. In particular,

a) It would be useful to include a table summarizing evidence for and against the potential modes of action by which TCE causes liver, kidney and lung cancer. This would include which metabolite has been demonstrated or is suspected to operate through which specific mode(s) of action and at what exposure levels.

b) In discussing the various metabolites and their related reactions, a comprehensive metabolic pathway should be given. There was the mention of Figure 2-1 (page 2-1, line 2) in which TCE metabolic pathways and those from chemicals sharing some TCE metabolites were presumably given. However, Figure 2-1 is missing from the draft assessment. This should be rectified. Figure 3-1 on page 3-57 achieved part of that purpose; however, the sharing of part of the metabolic pathway by other chemicals should be explicitly indicated.

A summary sentence or paragraph would often be helpful at the end of long text discussions of alternative hypotheses in order to clarify EPA's overall conclusion about likely modes of action for different metabolites and toxic effects.

The Panel notes that the current draft assessment, in discussing the effects of metabolic interactions, emphasizes the possibility that these interactions will increase toxicity. This is not necessarily true. Various alternatives should be discussed. Since it is commonly accepted that TCE metabolites are the more toxic species, the overall TCE toxicity might decrease to the extent that this would lead to some increase in the exhalation or urinary excretion of unchanged TCE. On the other hand, if TCE concentration increases in the blood because the P450 pathways are partially saturated, the amount of TCE processed via the GST pathway would be expected to increase, leading to greater internal exposure to renal toxic metabolites. The Panel advises the Agency to evaluate where evidence exists regarding such competitive inhibition of TCE.

The Panel also notes that, although the draft assessment did a very good job of exploring different pathways, there may have been too great a tendency to focus on the individual actions of particular metabolites, in part because key informative experiments have most often been done by administering either TCE itself or specific metabolites by themselves. The draft assessment, however, does usefully note that no one metabolite may be totally responsible for specific toxic actions. Therefore, there should be continuing research both on pharmacokinetic and pharmacodynamic interactions between TCE, TCE metabolites, and possibly other environmental toxicants.

The Panel recognizes that, given the current state of knowledge, there is uncertainty about which metabolites cause specific adverse effects and in the sequence of biological changes that lead to tumor development. Consequently, it is recognized that there would be substantial uncertainties associated with extrapolations of hypothetical mechanisms (or modes of action hypotheses) across species.

In conclusion, the Panel reiterates its commendation of EPA for an extensive evaluation of different modes of actions in the current document. However, the Panel strongly advises the Agency to add a more thorough quantitative evaluation of dose response relationships and dosimetry to its discussion of the role of different metabolites and multiple modes of action. Quantitative data are available in the literature that can improve characterization of mode of action in terms of cross-species and low dose extrapolation. More extensive use of this information can improve scientific understanding and strengthen the basis for decisions on cancer classification and the final risk assessment approach.



AR100181

# 4. CHARGE QUESTION 2

## 4.1. Agency Charge Question and Suggested Areas for Inquiry

Charge Question: Is the cancer weight-of-evidence characterization adequately supported?

Suggested Areas for Inquiry: The cancer characterization is based on both epidemiological and animal studies. Does the draft assessment adequately characterize the strength of the epidemiologic evidence and adequately address questions concerning the analysis by Wartenberg et al. (EHP 2000) and its inclusion of the Henschler study? Does the draft assessment adequately present and consider the animal evidence of tumors at multiple sites and its relevance to humans?

## 4.2. Panel Response

The Panel commends EPA for compiling an extensive array of scientific literature that included over 80 epidemiological studies and hundreds of toxicological and mechanistic studies and for characterizing the evidence relatively clearly and cohesively. The Panel feels that the Agency's overall qualitative cancer risk characterization was reasonable based on: a) significant experimental evidence showing tumors at multiple sites in two species (rats and mice); b) epidemiologic evidence in humans showing associations between TCE exposure and several cancers including at several of the same sites seen in animal bioassays; and c) mechanistic data indicating relevance of experimental findings to humans. There was a suggestion that EPA clarify more explicitly for the public what is meant by a "weight-of-evidence characterization."

The Panel also advises the Agency to improve the characterization of the cancer weight-of-evidence by evaluating human and animal studies more rigorously using established Agency criteria for evaluating studies of those types. On a related issue, several panel members noted that the assessment could be strengthened if the Agency emphasized and integrated information about dose-response and if it presented a coherent analysis of quantitative information available on the mode-of-action of metabolites. The Panel also advises the Agency to provide a more thorough discussion and critical evaluation of the conflicting human epidemiological evidence for kidney tumors.

### 4.2.1. Cancer Classification for TCE

The Panel did not receive a charge question from the Agency regarding the cancer classification for TCE, and thus it did not discuss that topic at length or agree on the cancer classification. Instead, the Panel agrees on the need for the Agency to evaluate the different lines of evidence for each tumor type in a more integrated manner. Some members advised that the Agency give special attention to more rigorous quantitative evaluation of exposure levels in human and animal experiments. Specific recommendations are presented in the subsections of this report below.

The Panel also notes that it was informed by Agency Staff at the panel meeting on June 18-19, 2002, that EPA was currently revising its cancer guidelines and that the Agency intends to apply to the final TCE assessment whatever guidance exists at that time for cancer characterization.



AR100182

In the course of discussion of several charge questions, panel members briefly discussed their different individual views of the cancer classification, and acknowledged there was a large policy component to the question of cancer classification. Panel members differed in their interpretation of how to apply the draft revised cancer classification guidelines and some requested clarification of the EPA cancer guidelines classification scheme before they could form a personal opinion. Several panel members characterized the weight-of-evidence as "very strong" and spoke in support of the Agency's proposed designation of TCE as "highly likely to be carcinogenic to humans." Several members, however, also suggested that the chemical could come closer to being classified as "known to be carcinogenic to humans." These panel members based their views on the animal cancer data showing tumor induction at multiple sites in two species, epidemiological data showing associations between exposure to TCE and excess cancer incidence among occupational and environmental cohorts, including several sites where tumors were induced in experimental animals, and mechanistic data showing similar metabolic pathways in animals and humans and a high incidence of a specific point mutation in the von Hippel-Lindau tumor suppressor gene in kidney cancer patients who had been exposed to TCE. In addition, Panel members noted that there are no data showing that the shape of the dose-response curve is different at environmental exposures versus at occupational exposures that are associated with increased cancer risks.

Another view expressed was that the Agency's characterization was not adequately supported by quantitative data and that a more appropriate characterization was "likely to be carcinogenic in animals at high doses, not likely to be carcinogenic in humans at lower doses." More specifically, in this view, TCE was seen as not likely to be carcinogenic in humans at lower doses for liver tumors and likely or suggestive to be carcinogenic for kidney tumors.

### 4.2.2. Human Epidemiological Studies

Among the epidemiological studies, the data appear strongest overall for liver cancer and also, to some degree, for lymphoma. All Tier 1 studies show excesses of liver cancer, yet two key German studies (Henschler, 1995 and Vamvakas, 1998) show excesses for kidney cancers, but did not address liver or lymphoma. There was a request for more data on exposure-response relationships for liver cancer from the Tier 1 studies and the Vamvakas study, and for more discussion of the liver cancer endpoint generally, since it was felt to be so strong. Tier 1 studies show excesses for Hodgkin's disease, non-Hodgkin's lymphoma, and multiple myeloma. The addition of a recently published study by Hansen et al., significantly adds to the weight-of-evidence for lymphoid tumors.

The Panel does have some concerns about the strength of the evidence for the kidney cancer endpoint based on the available epidemiological data. The uncertainty focused primarily on the study by Henschler et al. Concerns included: a) this study originated as a cluster investigation, thereby potentially introducing bias; b) the variability of underlying population rates for kidney cancer in German and Danish cancer registries; c) the magnitude of the indicated risk which was far out of proportion to risks observed in most other studies; and d) the significance of the Henschler study in light of the whole epidemiology database.[2]

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[2] Further analysis by a panel member showed that if one deletes the two early cluster cases then there are 2 RCCs and 1 renal pelvis cancer. In the US 10% of SEER ICD 189 cases are renal pelvis and thus the expected number of cases of RCC is about 1.3-0.13=1.2 for the current GDR registry (1988-89). This yields a non significant SMR of 2/1.2=1.7 . The inclusion of the 2 early cluster cases takes us to a biased high SMR estimate of 3.3 which is not significant either. If one accepts that the Germans are more like Danes the expected number of cases is less and the SMR using the cluster cases becomes significant. Finally it should be mentioned that the Henschler study employed



AR100183

There was agreement that the inclusion of the Henschler study introduces significant heterogeneity onto the overall meta-analysis of the renal cancer endpoint. In addition, the Panel notes that the Henschler study did not report any excess in liver cancer, thereby making the study less credible in light of the rest of the epidemiological literature. In defense of the Henschler study, several panel members raised the following points: a) in Germany, people frequently remain in the same workplace for many decades, thereby potentially increasing the total lifetime exposure in this cohort; b) from the description of the workplace, the exposures may have been very high compared to other studies; c) the results were directionally consistent with the Vamvakas study (1998) although not as strong, somewhat consistent with the recently published study by Pesch et al., and in line with the animal toxicology and mechanistic data (including the apparent over 10-fold increased risk reported among exposed workers with active forms of two GST genes) (Brüning et al, 1997a); and d) the very high TCE exposure may saturate P450 pathways thereby shunting the TCE toward the GST pathway and if that is the case, it is likely that kidney tumor may predominate.

Some members pointed to the history of cancer clusters in identifying other significant occupational carcinogens (e.g. asbestos, bis-chloromethyl ether, vinyl chloride). In these instances, the increased incidence in tumors associated with these other chemicals in one epidemiological study was replicated in other epidemiology studies. In the end, despite the uniqueness of the Henschler study, the Panel does not advocate omitting it from the draft assessment.

Several panel members said that the Henschler study should be omitted from consideration only if it were to become fairly clear that there is some other factor that would explain the elevated incidence and mortality from renal cancer in this cohort. In that case, the Agency could use the Finnish and Danish studies with liver and lymphoma as end points, and then simply discuss kidney, prostate and cervix without quantification of risk. The Panel recommends EPA include this study in the overall weight-of-evidence, taking into account information on exposure levels, and to address concerns regarding the Henschler study (1995a) and to discuss the results in light of competing lines of evidence including the recently published Danish study.

The Panel advises EPA to identify more clearly and then explicitly apply criteria for the selection of studies. EPA should select the broadest possible array of studies for each endpoint meeting those criteria, taking into consideration study design, availability of exposure estimates, and the goal of protecting health.

Panel members endorsed the division of the cohort studies into three tiers, and recommended that EPA explicitly weight the Tier 1 cohort studies (and case control studies that specifically focus on TCE) more strongly than the other studies that involved exposure to a variety of chemicals. Although there was some debate about the relevance of the Tier 3 dry cleaner/laundry worker studies, there was support for continuing to include these studies because many of the metabolites of PCE and TCE are the same. These dry cleaner studies, however, should not be weighted heavily in the overall weight-of-evidence assessment.

Several members suggested including discussions about prostate cancer and childhood leukemia, as there is limited epidemiological evidence to support both of these endpoints. In the case of prostate cancer, all the Tier 1 cohort studies showed slight increases in relative risk,

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cohort screening using abdominal sonography which should yield a higher incidence of tumor than expected from a population based cancer registry.



AR100184

leading to questions about a possible weak tumorigenic effect in humans. In the case of childhood leukemia, this disease has shown up in numerous community-based studies. In case control studies of childhood leukemia, parental occupation in a solvent-exposed industry is a consistent positive association (although the link specifically with TCE is unclear). Childhood leukemia would not be expected to show up in the occupational cohort studies because these studies did not evaluate offspring. In addition, the Panel recommends EPA add a discussion of the Hansen (2001) study, which adds scientific weight to the lymphoma and cervical cancer endpoints, but not to the kidney cancers, and of the recent Pesch study that found a slightly increased risk of kidney cancers. There was also a recommendation for a discussion in this section of glutathione S-transferace (GST) polymorphisms and their possible role in creating susceptible subpopulations for kidney cancer (Brüning et al., 1997).

Some panel members had criticisms and concerns about the Wartenberg review article (2000). In particular, the following points were raised. Wartenberg et al. adjusted the lower bounds of the confidence intervals of the reviewed studies; such an adjustment can be misleading and lead to results that appear to be more significant than they are (if the results need to be symmetrical on the log scale, the upper confidence bound could be lowered instead, or the confidence intervals could simply have been presented as published by the original authors without impeding the ability to calculate the variance of the log of the SMR). The Wartenberg review included blanks (dashes in the tables) for some endpoints where no cases occurred in the original studies even though some were expected; this could bias the overall analysis toward finding an effect. In at least one case (Henschler brain tumors), risk numbers for the exposed group were reported even though the risks in the unexposed group in the same study were actually higher. Finally, the separate calculations of incidence and mortality resulted in some cancers being counted twice, once in the incidence summary statistics, and again in the mortality summary statistics.

The Panel agrees that some of the key underlying studies need to be directly examined by the Agency and potential biases and errors should be addressed and corrected. Epidemiological data merit special attention because they may be potentially important in terms of population-attributable risk. In that context, the burden is on EPA to make decisions about which studies to weight most heavily with an eye toward justifying the decisions scientifically and protecting the public health.

There was a discussion of the pros and cons of performing a formal meta-analysis of the TCE cancer studies. While several panel members advocated a more traditional meta-analysis of the Tier 1 studies, because it would convey more clearly how individual studies were weighted, others pointed out that the study designs were perhaps too disparate, and that a meta-analysis would simply demonstrate a lot of uncertainty and would add very little information. The Panel advises the Agency to use criteria in weighing the overall epidemiological evidence and to provide tables summarizing critical information for each key epidemiology study including type of study, number of subjects, sources of exposure information, years and estimated levels of exposure, and basis for the estimated exposure levels.

### 4.2.3. Animal Toxicology

The Panel agrees that TCE is an animal carcinogen, although its potency is relatively weak. Tumors are observed in multiple organs of multiple strains of two species at relatively high doses. In the rat, TCE has been observed to cause a low incidence of rare kidney tumors at high doses (in the presence of renal toxicity), which should be considered treatment-related. TCE also causes Leydig cell tumors in the male rat, another effect that is likely to be treatment-related. In the mouse, liver tumors occurred primarily by gavage rather than by inhalation, and

these are considered to be treatment related, as are the lung tumors after exposure by the inhalation route.

Although human studies show excess for lymphomas, lymphomas in the mouse are more problematic. These were increased in 3 out of 6 studies, but may only be treatment-related in one study, because the NTP study showed the control was somewhat low and the incidence in the treatment group fell within the range of historical controls. Other panelists pointed out that while historical controls are a useful comparison, the study controls were in an acceptable range and that the elevated rate of lymphoma in the treated animals should not be dismissed. There was a suggestion that EPA reexamine the mouse lymphoma data to see if the endpoint is treatment-related. If EPA decides the mouse lymphoma endpoint is treatment-related, then a discussion reflecting the issues with the NTP studies should be added. In general, many of the carcinogenicity studies that were considered negative are not included in the tables and all studies for each tumor type should be included. In terms of site concordance, none of the tumors observed in rats were observed in mice and vice-versa.

There was discussion about the genotoxicity issue with multiple viewpoints expressed on the likelihood of genotoxicity. Most panelists agreed that genotoxic mechanisms are plausible for some metabolites.

Many panel members supported the conclusions concerning the genotoxicity of TCE and its metabolites, as discussed by Moore and Harrington-Brock (2000). They concluded: the weight-of-evidence argues that chemically induced mutation is unlikely to be a key event in the induction of human tumors that might be caused by TCE or its metabolites. This conclusion draws from the fact that these chemicals require very high doses to be genotoxic. The exception is DCVC, the glutathione conjugate of TCE. Moore and Harrington-Brock (2000, Page 221, 1st paragraph) conclude that the potency of DCVC is unknown "because there are no data for mammalian cells from in vitro or in vivo experiments." Thus, while the weight-of-evidence indicates that most of the tumors induced by TCE are unlikely to be due to a mutation event, it is not possible to exclude this possibility.

Other panel members were concerned about the remaining possibility of genotoxicity. One panel member raised the issue of a transient epoxide intermediate that may be formed in the first metabolic step in the oxidative pathway because the oxidative metabolites TCA and DCA are derived from this intermediate. There is some evidence that this may occur, and the issue is discussed in the Lash paper (2000), but this issue is not even mentioned in the EPA draft assessment. Another panel member raised the issue of the mutagenicity of chloral hydrate as another controversy that bears more discussion in the draft assessment. Several panel members advocated strengthening the discussion of genotoxicity in the draft assessment.

Another view expressed was that the genotoxic hypothesis needed to be more carefully and quantitatively examined by the methodology described in the response to Question 1. Panel members overall, held somewhat different views on the weight that should be given to genotoxic modes of action for the liver tumors Panel members felt it was important to keep evaluation of the genotoxic hypothesis in the mix of possibilities.

For liver tumors, several hypotheses are discussed in the EPA draft assessment, including: peroxisome proliferation, disturbances in cell signaling and carbohydrate metabolism, and DNA damage. TCA and DCA likely account for the liver tumor response to TCE, but have different characteristics. TCA is more potent than DCA and has a greater sustained peroxisome proliferation effect. TCA and DCA, when given individually, result in tumors that are phenotypically different. An explanation is that DCA and TCA may selectively modify the

growth rates of different clones of cells via altered cell replication and apoptosis rates. Many scientists agree that TCA and DCA are hepatic tumor promoters (a term that is avoided in the draft assessment) that exert their effects through cell proliferation and death. Different tumor promoters select different subpopulations of hepatocytes that are clonally expanded. In the draft assessment, there is considerable discussion of effects of TCE and its metabolites on carbohydrate metabolism. One panel member viewed this discussion as speculative, and felt that the significance of this mode of action is not really clear. One of the problems with DCA is that it is not measurable after the administration of TCE, but modeling studies indicate that there is sufficient exposure. The conclusion is that both TCA and DCA contribute to the hepatocarcinogenicity of TCE in mice at high dose levels and that chloral may also be involved.

For rat kidney cancers, there was agreement that the draft assessment characterized alternative modes of actions. There were differences among panel members about whether the scientific evidence was sufficiently strong to support a mode of action for kidney tumor formation based on the GST metabolite. Some panel members believed that the mode of action of the kidney cancers was likely to be primarily through the GST metabolite, DCVC, a known mutagen and cytotoxic chemical, and that this mode of action was relevant to humans. In this view, peroxisome proliferation and alpha 2u-globulin were unlikely modes of action in the kidney. From this perspective, the cytotoxic and mutagenic effects of DCVC following its activation by renal beta-lyase was the likely mode of action for kidney tumor formation. The finding of DCVC in blood of human volunteers exposed to TCE and the presence of beta-lyase in the human kidney provided additional evidence that the GSH-mediated pathway was operable in humans. An alternate view on the panel was that the EPA document did not include critical information to fully characterize the weight-of-evidence for kidney tumor formation in rats. Information that would be helpful would include the extent of kidney toxicity and mortality observed at dose levels causing the low incidence of kidney tumors and the dose-response relationship of TCE and key metabolites relevant to the different modes of action. The EPA document could benefit by including consideration of the analytical discussion provided in Lash et al. (2000) that weighs the evidence regarding different possible modes of actions in relation to the dose-response relationship at likely human exposure levels of TCE.

There was agreement that EPA appropriately characterized a need for further research on mouse lung tumors. One hypothesis is that mouse lung tumors are due to the formation and accumulation in the Clara cells of Chloral Hydrate (CH) formed via CYP2E1. CYP2E1 and Clara cells are higher in mice as compared to rats and humans suggesting a species difference in sensitivity. There is a need to demonstrate that CH is responsible for lung tumor development, since CH is clearly clastogenic and mutagenic at high doses, suggesting that both genotoxicity and cytotoxicity may be involved. There is debate about the relevance to humans of the rat Leydig cell tumors, which might be expanded and improved by a fuller discussion, including a discussion of rat Leydig cell tumors in the draft assessment, with a reference to the paper by Cook et al., which discusses the basis for differences in responsiveness between rats and humans.

The overall toxicological assessment was that the rat kidney cancers are relevant to humans. There was some scientific difference of opinion about the human relevance at low doses of the lung and Leydig cell tumors. Regarding the mode of action, panel members agreed that a genotoxic mode of action is plausible for kidney tumor formation based on the currently available evidence, although there was a difference of opinion about the likelihood that a genotoxic mode of action exists for TCE. Overall, the Panel recommends that EPA expand the discussions about some of the main scientific controversies, with some more references to the primary scientific literature in selected cases involving critical studies.

## 5. CHARGE QUESTION 3

### 5.1. Agency Charge Question and Suggested Areas for Inquiry

Charge Question: A new feature of the cancer database is molecular information on the von Hippel-Lindau (VHL) tumor suppressor gene. Is this information adequately discussed and are the conclusions appropriate?

Suggested Areas for Inquiry: Does the draft assessment adequately present alternative interpretations of the von Hippel-Lindau findings and identify this as a research area that would help resolve an open question about TCE and kidney cancer?

### 5.2. Panel Response

The consensus of the Panel is that the discussion in the draft assessment is generally appropriate. There was a recommendation to strengthen the description from the "suggestive evidence" referred to on line 8 of page 3-38. The Panel generally agreed that EPA is wise not to regard the evidence as entirely conclusive pending independent confirmation. The discussion in the draft assessment might be improved by including some additional comparative observations from kidney cancers not in the TCE exposed workers. Panel members offered the following enhanced discussion as a starting point for EPA consideration.

Mutations in the VHL tumor suppressor gene (both germline and somatic) have been associated with increased risk of renal cell carcinoma (RCC). Recent studies by Bruning et al. (1997) and Brauch et al. (1999) provide evidence that TCE exposure may be associated with VHL mutations among RCC patients. Specifically, Bruning et al. examined VHL mutation by single strand conformation polymorphism (SSCP) in renal tissue, initially from 23 RCC patients with documented high occupational TCE exposure. All (100%) of this first set evidenced VHL mutation, which the authors concluded was higher than the background frequency of 33% - 55% among TCE-unexposed RCC patients. In a follow-up, Brauch et al. determined VHL mutation frequencies by SSCP and direct sequencing of mutations in renal tissue from 44 TCE-exposed RCC patients. 75% of TCE-exposed patients had mutations in VHL and 39% had a "C to T" mutation at nucleotide 454. (All "C toT" transitions in the control renal cell carcinoma patients were evidently relatively rare at about 6% total incidence based on combined data from several authors.) VHL mutations were detected by Brauch et al. in workers with medium and high but not low TCE exposure. However, only 3 patients were classified as having low exposure. Overall, these data indicate a highly significant association ($p=0.0006$) between TCE exposure and multiplicity of VHL mutations.

The authors of this paper did not measure total VHL mutation frequency among TCE-unexposed RCC patients, but used a restriction endonuclease-based assay to evaluate the specific "C to T" mutation at nucleotide 454 among 107 unexposed patients. None of the TCE-unexposed RCC patient had the "C to T" mutation at nucleotide 454, indicating a mutational hot spot in VHL associated with TCE-exposure. The apparent elevation in the frequency of renal cancers with this specific mutation is indicated to be at least six-fold, and is likely to be 40-fold or more.

Applying a Poisson distribution to the occurrence of this specific mutation in the studied groups, the finding of zero cases in 42 VHL mutation bearing tumors in the control group can be used to rule out a true incidence of as much as 3 cases in 42 (or about seven percent) with 95% confidence. Therefore, a conservative estimate of the relative enhancement of the frequency of



AR100188

this specific mutation in the renal cancers from the trichloroethylene exposed workers is 39%/7% or just over 5.5-fold. If we take as a plausible but very tentative "best estimate" incidence of 0.5 of these mutations in 42 mutation-bearing controls examined (about 1%), then the indicated enrichment of the specific mutation is about 39%/1% or just under 40-fold. The true enhancement could, of course, be even larger than this, but that could only be determined by observations with a much larger sample size.

Follow-up studies are needed to confirm the association between TCE and mutations at nucleotide 454 and to compare total mutation frequencies in VHL gene among RCC patients with and without TCE exposure, as there is uncertainty over the background rate of VHL mutations in RCC. Nonetheless, the Agency's conclusion that these findings appreciably "augment" the characterization of TCE as highly likely to produce cancer in humans (3-51) is appropriate.

The importance of these observations is reinforced by finding an association of the VHL mutations with loss of heterozygosity at the VHL locus (Brauch et al., 1999), making a strong analogy with the classic case of changes in both copies of the retinoblastoma gene in the causation of retinoblastoma. If the hot-spot and other VHL mutations found in the worker studies are in fact inactivating mutations coupled with loss of heterozygosity indicating inactivation of the homologous VHL gene on the opposite chromosome, then the inference must be that these mutations are not just indicators of TCE exposure, but are likely to be directly on the causal pathway for the kidney cancers. The Panel suggests that EPA address this issue in the draft assessment.

Another suggestion for the Agency to consider is that the discussion could be improved by more clearly defining the "alternative" hypothesis (lines 26-28 on p. 3-38) about some selection mechanism that could account for these observations without involving mutagenesis by a TCE metabolite. Certainly it is conceivable that the overtly toxic conditions of high level TCE exposure could lead to differential growth vs. death/differentiation rates for cells with particular mutations. But the mutations must be present in the cell population in order to be selected and the toxic metabolite of TCE that is formed in the kidney is also reactive with DNA, suggesting the potential involvement of mutational events.

To date, there is no supplementary information on the implications of this particular mutation (other than probably repressing VHL gene function, which is likely to be a property of many other tumor-associated mutations as well) that supports the idea that cells possessing this mutation would have a selective advantage over cells possessing other VHL-inactivating mutations. The most likely alternative hypothesis is that somehow cells with this particular VHL mutation have an enhanced selective advantage in the TCE-influenced kidney environment before the final mutagenic steps leading to fully developed tumors have occurred. The differential selective advantage might lead to a larger clone of precursor cells (relative to precursor cells with other VHL mutations) in which the final mutagenic steps leading to cancer can occur.



AR100189

# 6. CHARGE QUESTION 4

## 6.1. Agency Charge Question and Suggested Areas for Inquiry

Charge Question: Does the assessment adequately discuss the use of multiple critical effects in developing an oral reference dose (RfD) and inhalation reference concentration (RfC) for effects other than cancer? Are the uncertainty factors well discussed and well supported?

Suggested Areas for Inquiry: The RfD and RfC were developed after considering both human and animal studies. Does the draft assessment adequately characterize the data at each site of toxicity and focus on an appropriate subset of critical effects? A key issue is the application of uncertainty factors. Alternative views range from use of fewer uncertainty factors to use of additional uncertainty factors to reflect studies showing reproductive effects and enzyme differences between children and adults. Does the draft assessment adequately discuss and characterize the evidence supporting alternative positions as it arrives at an RfD and RfC?

## 6.2. Panel Response

### 6.2.1. Multiple Critical Effects: Does the draft assessment adequately characterize the data at each site of toxicity and focus on an appropriate subset of critical effects?

The draft assessment summarizes many epidemiological and experimental studies and identifies the Lowest-observed-adverse-effect levels (LOAELs )/ no-observed-adverse-effect levels (NOAELs) for multiple critical effects to aid in development of a single point of departure. The Agency's consideration of multiple noncancer endpoints in both the general discussion and in the derivation of the RfD and RfC is commendable. TCE clearly has important hepatotoxic, nephrotoxic, neurotoxic, immunologic, developmental, and reproductive effects that should be considered in the derivation of the RfD and RfC. The use of multiple critical effects increases one's confidence that the point of departure dose is at the low end of doses at which adverse effects can be observed.

Some panel members suggested that the characterization of the data at each site of toxicity could be strengthened considerably. In the opinion of some panelists, the current discussion lacks the type of critical analysis and discussion of the weight-of-evidence that is necessary to understand the Agency's rationale for selection of endpoints, level of concern, dose-response extrapolation, effect of time-duration on key endpoints, and application of uncertainty factors. Other panel members thought the discussion of non-cancer effects and discussions surrounding the development of the RfD and RfC were quite good and that with relatively limited additional clarification the non-cancer section of the draft assessment would be complete.

The general recommendations for improvement of Section 3.4. of the draft assessment are identified immediately below. Detailed comments on specific endpoints that are important for EPA to consider can be found in Appendix A to this report.

a) The Panel advises the Agency to discuss the key studies in Section 4 and listed in Table 4.2 in greater detail to outline the scientific basis for selection of endpoints for derivation of the RfD and RfC. At present, some of the critical studies in Table 4.2 that are used to derive the RfD/RfC are not discussed at all in Section 3.4; others are given only a cursory mention. This is a striking deficiency in the draft assessment that prevents EPA's rationale for deriving the RfC and RfD from being clearly understood.



AR100190

b) The discussion of the specific toxicity endpoints in Section 3.4 does not provide the essential information that is necessary to understand the Agency's rationale for selection of point of departure, level of concern, or uncertainty factors. Although a lengthy detailed examination of the different studies is not appropriate, a more critical evaluation of the data is needed. At a minimum, scientific data such as exposure levels, severity and nature of effects, methods used to detect effects would be useful. The Panel suggests that EPA include tables of studies discussed for each organ toxicity discussion. These tables could include information on species, number of subjects/animals, doses used, route and duration of exposure, and type of effect noted at each dose. Additional information useful for human studies includes type of study (e.g. cohort, case control, cross sectional, ecologic, prevalence), source of control population, method of establishing exposure levels, and possible exposures to other chemicals. Finally, discussion of data, especially pharmacokinetic and pharmacodynamic data that assist in understanding relative sensitivity of humans and animals, human variability, and responses relative to duration of exposure could be highlighted in order to provide a stronger scientific foundation for later discussions on uncertainty factors. This type of balanced critical evaluation would strengthen the scientific data necessary to support the Agency's derivation of the RfD and RfC.

c) An improved critical analysis and discussion (as outlined in point 2) of key developmental studies and other studies evaluating different life-stages should be integrated into each toxicity section. It will be important to highlight any data and relevant mechanistic data that will aid in understanding relative sensitivity of different life-stages. These discussions will then provide a strong scientific basis for a separate section devoted to summarizing and integrating discussion of the different developmental effects.

d) The Panel notes that although EPA has evaluated information on metabolism, pharmacokinetic and mode-of-action data for TCE related to cancer endpoints, it has not extended this scientific discussion to non-cancer endpoints of TCE toxicity. For example, several toxicity sections include *in vivo* and *in vitro* studies on TCE metabolites, but fail to provide the essential information on doses used in these studies compared to occupational or environmental human exposure levels. This information would be helpful in understanding the appropriate use of this data for dose-response analysis and in assessing TCE toxicity at relevant human exposure levels.

e) The mode-of-action discussion is focused primarily on cancer endpoints. A more rigorous discussion of background would be helpful for each critical endpoint as it relates to mode of action. Each endpoint may have different modes of action involving potentially different key metabolites that need to be taken into account separately in considering background cumulative exposures. We note that Table 2-1 lists data sources for estimated adult exposures, but the references cannot be found based on the numbering system provided.

f) The Panel advises EPA to develop its assessment from the set of well-conducted studies that make a difference to the weight-of-evidence. Evaluation of the quality of the study using criteria developed by EPA for adequacy of studies (U.S. Environmental Protection Agency, 2002b, page 4-6 to 4-8) is especially important to understand the strengths and weaknesses of different papers cited. Additional studies that should be integrated into the critical evaluation of the weight-of-evidence are by Fisher et al. (2001) and Albee, R. (1993, 1994). Any other well-conducted studies on TCE, especially those conducted under Good Laboratory Practices that have been submitted to EPA, need to be evaluated by these criteria.

The Panel is providing these general comments as major areas that should be addressed for each of the noncancer endpoints. Specific comments on noncancer endpoints are provided in

Appendix A to this report. Section 1 of Appendix A addresses one of EPA's proposed areas of inquiry: Does the draft assessment adequately characterize the data at each site of toxicity?

### 6.2.2. Modes of Action of TCE Toxicity

The mode-of-action discussion in the draft assessment focuses on cancer. However, the discussion is also important to the non-cancer toxicity. The draft assessment needs to provide a balanced discussion of the role of TCE and metabolites in the mode of action of TCE toxicity. Bull (2000) concluded that DCA is unlikely to contribute to the induction of peroxisome synthesis at levels that are produced by the metabolism of TCE. Barton and Clewell (2000) conclude that there are two major hypotheses for the mode of action of TCE in the causation of neurological effects: the activity of parent TCE, or the metabolite, TCOH. In their opinion, DCA is not considered to play a role. While some panelists believe the role of DCA in non-cancer endpoints such as neurotoxicity is overstated in the draft assessment, given these conclusions of the state-of-the-science papers, others were not convinced that the state-of-the-science papers are correct on this point and found it reasonable for EPA to consider studies involving DCA. In addition, the discussion of TCE metabolism needs to include the impact of exposure levels on the kinetics of TCE metabolism and compare and contrast what is known about the kinetics at the high doses studied, compared to environmentally relevant levels.

### 6.2.3. Uncertainty Factors - Areas of Agreement and Differences Within the Panel

The Agency suggested that an area for inquiry for Charge Question 4 was the use of uncertainty factors. The Agency asked: "Does the draft assessment adequately discuss and characterize the evidence supporting alternative positions as it arrives at an RfD and RfC?"

The Panel advises the Agency to explain more clearly in the draft assessment how uncertainty factors were derived for the RfD and RfC. The draft assessment does not adequately discuss and characterize the evidence supporting alternative positions in deriving these values. The assessment should address the public comments from the authors of the state-of-the-science papers regarding these alternative positions.

The Panel also agrees that discussion of uncertainty factors in the document is complex. Multiple factors were chosen by the Agency for the RfD and the RfC, and several charge questions were posed to the Panel related to these factors. The Agency's draft factors and related charge questions are summarized in the table below.

As the Table notes, several Charge Questions, and therefore several parts of this Panel report relate to the issue of uncertainty. The Panel finds it difficult to isolate separate aspects of the uncertainty issue not only because they are logically related, but also because the composite uncertainty factors derived from their product will be used to calculate the RfD and RfC and will have a major impact on risk management decisions. The Panel also notes the policy constraints mentioned in the draft assessment (p. 4-10), which stated that EPA has limited the RfDs calculated using conventional 10-fold uncertainty factors to 3,000 when human-equivalent doses are used. EPA in its draft assessment then limited the composite uncertainty factor for TCE to 3,000.



AR100192

**Table 1**
**Summary of Uncertainty Factors in the Draft Assessment and Related Charge Questions Posed to the SAB**

| Uncertainty Factor | Draft Value for the RfD | Draft Value for the RfC | Related SAB Charge Question and Related Section of this Report |
|---|---|---|---|
| Human Variation | 50 | 10 | Question 8; Section 10 and Appendix A |
| Children's Uncertainty factor[3] | | | Question 9; Section 11 |
| Subchronic-to-Chronic uncertainty | $10^{.5}$ | 10 | Question 4; Section 4 and Appendix A |
| LOAEL-to-NOAEL uncertainty | $10^{.5}$ | 10 | Question 4 Section 4 and Appendix A |
| Other Factors[4] | $10^{.5}$ | No factor used | Question 7; Section 9 and Appendix A |
| Composite Uncertainty Factor | 3,000 | 1,000 | |

Given this policy constraint and the Agency's application of standard uncertainty factors (draft assessment, p. 4-7) to TCE, the Panel found itself--and the Agency-- far from an ideal situation for the risk assessment. In an ideal situation, there would have been data for different endpoints and different populations or different pharmacokinetic variability "uncertainty factors" for different endpoints and different populations. The Panel observes that this would be a useful topic for future research. Ultimately, the whole system of uncertainty factors could be usefully revisited and defined in terms of an objective of achieving x level of risk for the yth percentile of the variable human population with z degree of confidence.

Given the limitations of current data and methods, there were several alternative views held within the Panel about the uncertainty factors chosen and their relationship to composite uncertainty factors. These views are discussed immediately below and also discussed in the sections referenced in Table 1.

One concern involved the derivation of the RfD and the RfC. In deriving those values, EPA chose to apply uncertainty factors to "point-of-departure" doses. These were derived as composite values, representing the lowest human equivalent doses at which several of the critical studies identified adverse effects and including uncertainty factors based on different endpoints. For example, the RfD was based on liver-to-body weight changes, but subchronic to chronic

[3] Although a Children's uncertainty factor is listed separately in this table to highlight the issue of whether EPA should explicitly develop a quantitative uncertainty factor for children, the reader should note that the Panel was informed by EPA during the TCE Public Teleconference on July 18, 2002 that the Uncertainty Factor for Human Variation was designed to include variation due to different life stages. This is consistent with the discussion of uncertainty factors in footnote 61, page 4-7 of the draft assessment

[4] Other factors to reflect professional assessment of scientific uncertainties not explicitly treated above, including completeness of the overall database, minimal sample size, or poor exposure characterization. In the case of TCE, a modifying factor of $10^{.5}$ was set to account for the difference between human background exposures to TCE and its metabolites compared to background exposures in test animals.



AR100193

uncertainty was derived from duration response trends for decreased testosterone, central nervous system toxicity, and other effects.

Several panel members felt that EPA should not apply uncertainty factors to composite "point of departure" doses, but should determine which uncertainty factors are scientifically justified based on the proposed mode of action for each of the critical effects separately. Then, these factors should be applied to the human equivalent dose for that particular critical effect; the most protective value resulting from these calculations could then be chosen as the RfD or RfC. These panel members also felt that evaluating key studies separately as outlined in Barton and Clewell (2000) was also an important exercise in making sure that decisions are internally consistent with the experimental study from which the NOAELs/LOAELs were derived. For example, applying an uncertainty factor for LOAEL to NOAEL conversion may be scientifically justified for the critical study that identified a LOAEL (Buben and O'Flaherty, 1985), but not for the critical studies that identified NOAELs (Tucker et al., 1982; Sanders et al., 1982; Maltoni et al., 1986). The scientific data available for TCE allow EPA to take a more systematic and rigorous approach to risk assessment as outlined by Barton and Clewell (2000)[5]. Specific recommendations regarding different uncertainty factors are discussed in Appendix A.

Another set of concerns involved children's susceptibility. One concern was that children's susceptibility was not included explicitly in the derivation of the uncertainty factors. Panelists felt that it made no sense to include in the document a discussion of ways that fetuses and children are more susceptible to TCE and then fail to account for this susceptibility quantitatively.

Many panelists advised the Agency to develop a children's uncertainty factor to account for this difference in susceptibility. Several panelists expressed concern that EPA initially derived a composite uncertainty factor for the RfD of 5,000, but reduced the factor to 3,000, because of policy precedents in setting RfDs. It was unclear which of the uncertainty factors discussed above was eliminated in order to come up with a total of only 3,000 instead of 5,000, and these panel members asked that this be clarified in the draft assessment. They considered it unscientific and inconsistent to build a composite uncertainty factor and then arbitrarily decrease it to bring it down below a level that the Agency considers acceptable. These panelists urged the Agency to use the full 5,000-fold uncertainty factor if all the components can be justified.

An alternative view was expressed by other panelists, who noted that a 3.5-fold difference between adults and infants for metabolism of TCE should have been included in the EPA analysis (Renwick, 1998). Given the large uncertainty factor of 3,000 already established for the RfD for TCE, these panelists suggested that this additional 5-fold uncertainty factor should be retained as one part of the existing "Other" uncertainty factor (either at the $10^{.5}$ value for this factor set in the draft assessment or another value to be set after reexamination of the supporting information) already allocated in the Agency's draft assessment to reflect "professional assessment of scientific uncertainties not explicitly" covered by other factors used (see additional discussion in Section 11 of this draft report). Another view was that the 50-fold human variability uncertainty factor that appears in the draft assessment for the RfD was probably large enough that an additional factor for children is unnecessary. However, an additional uncertainty factor for children may be warranted for the RfC, which is based largely

[5] In this state-of-the-science paper on TCE, Barton and Clewell provide a framework within which to make consistent scientific judgments regarding selection of critical studies, internal dose metrics, pharmacokinetic models, approaches for interspecies extrapolation of pharmacodynamics, and uncertainty factors for each critical effect.

on central nervous system effects in health adults and currently only includes a 10-fold factor for human variability.

Yet another view was that the discussion of children's uncertainty factor needed to be more closely linked to the critical endpoint under consideration. They recommended the approach of Barton and Clewell. Based on the critical endpoint of concern, decisions could be made regarding whether or not there is residual concern regarding risks to children. According to this view, these decisions should not be based on differences in exposure that will be routinely accounted for in the exposure assessment, but should be based on pharmacodynamic concerns specific to children based on the endpoint of concern. For example, the decision might be different for liver-to-body weight changes than for neurologic effects, depending on the severity and nature of the effects.

A similar set of alternative views emerged relating to uncertainty factors for background exposures. In light of the prevalence of such background exposures in the general population, many panel members thought it prudent to apply a modifying factor to the RfD, as proposed in the draft assessment. These panel members felt that in special cases, where data are available for estimating these co-exposures for all relevant populations, the modifying factor could be omitted. Some panelists agreed with the Agency's argument that, unlike the RfD, the RfC was largely derived from human studies, and thus already incorporated these background exposures (because the study subjects likely had similar background exposures as the general population). Therefore, it was a reasonable argument for not applying the modifying factor.

In contrast, other panel members did not agree with the application of a modifying factor for background exposures for either the RfD or RfC. Some expressed the view that it was inappropriate to use such a new groundbreaking approach for an individual chemical, prior to the Agency's finalizing a cumulative risk assessment approach (US EPA, 2002a) that provides a framework for taking background exposure into account. Since RfDs are often compared for priority setting, these panelists felt that a consistent approach to handling background be taken. A panelist noted that such an approach separate from the RfD approach has been successful for EPA's Office of Pesticide Programs. (See additional discussion of an uncertainty factor for background exposures in section 9 of this report).

Additional general comments relating to derivation of the RfD and RfC and LOAEL to NOAEL uncertainty for the RfD and RfC follow immediately below. More detailed comments with recommendations for improving the Agency's discussion and characterization of the evidence supporting alternative positions for use of uncertainty factors for deriving the RfD and RfC can be found in Appendix A.

The Panel provides the following general advice to the Agency in its discussion of and development of the RfD and RfC in a revised assessment for TCE.

a) The Panel advises EPA to clarify more fully the reasons for the differences in the uncertainty factors used in the RfD and for the RfC.

b) The Panel advises EPA to describe explicitly its underlying assumptions when choosing uncertainty factors based on knowledge of mode of action and to describe evidence for alternative mechanisms.

In the opinion of some panelists, EPA departed from common practice in applying uncertainty factors to point-of-departure doses that are composite doses derived from the

LOAELs and NOAELs of multiple critical studies with different endpoints and different study designs. Several members of the Panel expressed strong disagreement with EPA's approach and recommended instead the approach used by Barton and Clewell (2000), which considers each critical endpoint and applied uncertainty factors based on scientific knowledge of the mode of action for that endpoint. This approach would allow the RfD to be supported by all the available data, and in a transparent manner.

Several other panelists felt that the Agency's approach was justified on the basis of the currently available scientific evidence and for the purpose of ensuring adequate protection. They noted that one would not necessarily expect that all non-cancer health effects would occur at similar doses. In fact, normally some of the effects would be high dose, and others could occur at lower doses.

c) Uncertainty Factors for NOAELS and LOAELs. In regard to presentation and communication of the Agency's justification for choosing NOAELs and LOAELs, the Panel advises EPA to show step-by-step how NOAELs and LOAELs of the key studies were converted to human equivalent doses. The Panel advises the Agency to articulate clearly the scientific rationale for selecting the key studies. This is especially needed because these studies are not standard toxicity studies of duration and design that are typically used to set chronic RfDs and RfCs. Such a discussion would make the selection of the point of departure more transparent.

Improved tabulation of studies in Table 4.2. of the draft assessment, as described in Appendix A, Section 2.4 of this report will go a long way towards making the EPA's decisions more transparent. It will also help the EPA identify areas that require further discussion in the text.

In regard to the Agency's choice of NOAELs and LOAELs, the Panel represents a spectrum of views about: 1) whether an uncertainty factor for a LOAEL is needed; 2) the size of the uncertainty factor chosen; 3) the rationale for a difference in factors chosen for the RfD and RfC; and 4) why an additional uncertainty factor was added to the LED10 that was calculated using the benchmark dose approach. These issues and views are discussed in Section 2.4 of Appendix A. The Panel advises the Agency to provide a clearer discussion in the assessment of the spectrum of scientific views on these issues and a clearer justification for the decision made by the Agency.

There was, however, general agreement that if EPA decides to retain the uncertainty factors described for TCE in the draft assessment, it is important for EPA to spend the time and effort to develop the scientific rationale for these additional factors, so that this new approach is not regarded as arbitrary. For example, the available scientific data on pharmacokinetics may help to quantify the impact of background exposures at relevant human occupational and environmental exposure levels. Such justification would strengthen EPA's decision to include such derived uncertainty factors before the draft Framework for Cumulative Risk Assessment (U.S. Environmental Protection Agency, 2002a) is finalized.



AR100196

# 7. CHARGE QUESTION 5

## 7.1. Agency Charge Question and Suggested Areas for Inquiry

Charge Question: Does the assessment adequately discuss the derivation of a range of estimates for the cancer risk? Are there any studies that should/should not have been included?

Suggested Areas for Inquiry: There is some question about whether the draft assessment should condense the range into a single "point" estimate. Does the draft assessment adequately present the case for a range of estimates? A key question for each tumor site is the choice of a linear or a nonlinear approach based on the mode(s) of action at that site. Does the draft assessment adequately describe how the available data on mode of action would support either a linear or a nonlinear approach?

### 7.2.1 Panel Response

The Panel commends EPA for the derivation of a set of cancer risk estimates or cancer slope factors (CSF) for TCE in the draft assessment. The presentation of a range of estimates is a step forward for EPA towards a more explicit and more quantitative representation of the substantial uncertainties in estimates of cancer risks.

The Panel does not recommend reducing the range of CSFs into a single "point" estimate, either a geometric mean or another measure of central tendency. Reasons for not reducing the range of the CSFs into a single number have been given in the draft assessment sufficiently clearly and exhaustively.

On the surface, the estimation and the rationale underlying the presentation of a range of cancer estimates appear to be reasonable and informative. Further investigation of this new approach for risk assessment is, however, warranted

The Panel recommends that the Agency improve its presentation of the cancer slope factors and discussion of the scientific rationale for choices made. Several suggestions for improvement appear below.

#### 7.2.1.1 Clarification of the Cancer Slope Factors

The Panel discussed suggestions for clarification. They directly concern improving the presentation of the derivation of the risk estimates using the data available for TCE.

a) One obvious addition to the present content of the draft assessment should be a detailed presentation of how each study contributed to the set of cancer slope factors. All available information should be provided to enable other risk assessors to reproduce the derivation of the individual cancer slope factors used in the risk assessment procedure for TCE. The reasons for choosing a study should be explained and the type and wealth of data used for the cancer slope factors calculation should be described. The derivation of exposure estimates should be given and their strength and weaknesses should be discussed on a study-by-study basis. More detail on the exact calculations used would be helpful in a technical appendix. With such a presentation, the Agency would elaborate as transparently and as explicitly as possible the approach it has used for the derivation of each of the cancer slope factors in the draft assessment.



AR100197

This presentation should include several specific revisions of the:

1) Introductory statement , "Several cancer slope factors were developed, with most between 2x10-2 and 4x10-4 mg/kg-d."

2) Definition of the slope factor (pages I -7 and 4-15)

3) Explanation of the overall approach of deriving this set of alternative estimates (e.g., pages 4-1, 4-2).

EPA's own responses provided to the Panel in its "Summary of Public Comments for EPA's Science Advisory Board" with regard to Question 5 already contain valuable information that could be used in such a presentation.

b) It appears that calculations of exposures for the Finnish cohort (Anttila, et al., 1995) were based only on the urinary TCA measurements for the cancer cases (see page 4-16, line 13pp). If this is what was done, the exposure estimates should be revised to include the full group(s) of workers who were at risk - not just those who ultimately developed the cancers. Also, for the occupational epidemiological study-based calculations as a whole, it is not clear that there was a correction for the healthy worker effect (or the healthy worker survivor effect, whereby healthier lower-background-risk people tend to stay on jobs longer and receive greater exposures) (see page 4-16, line 26).

c) Public comments raised on the correct use of the clonal two-stage carcinogenesis model (Moolgavkar-Venzon-Kundsen two-stage model of carcinogenesis) for biologically based mechanistic modeling should be considered very carefully. The Panel advises the Agency to carefully document the description of the modeling itself and make the data used for this modeling available so that other risk assessors can replicate those evaluations. The Panel encourages research to improve biologically based mechanistic carcinogenesis modeling for TCE.

d) The Panel advises the Agency to discuss in the assessment (section 4.5.1.3) whether problems exist when the New Jersey Drinking Water Study (Cohn et al., 1994) is used.

e) The Panel finds that footnotes in Chapter 1 are very helpful for readers. More footnotes in other chapters would improve the discussion. For instance, there is a need to provide a fuller discussion of several points regarding Cancer Slope Factors, specifically:

1) p. 4-16, line 16, the number of 2.956.Where did it come from?

2) p. 4-18, line 28, genotype GSTM/GSTT

3) Table 4-1, the ratio of 97.5 percentile/2.5 percentile equals the span of the 95% confidence interval. What is meant exactly by this?

These are only some examples.

### 7.2.1.2 Suitability and Use of the Cancer Slope Factors

Several further issues need to be addressed, clarified or discussed for making the current derivation of the range of cancer slope factors better suitable for the risk assessment of TCE.



AR100198

a) The meaning of the "upper bound" figures quoted needs to be clarified (e.g. page 4-19, line 27-28). Are these 95% confidence upper bounds considering only the statistical sampling error? What additional uncertainty would be expected from the uncertainty in the estimates of long term exposures? Can upper bounds on the cancer slope factors be defined for human exposure?

b) Estimates of cancer risks for different target organs should not be seen as alternatives to one another; but such risks should be probabilistically additive for the typical person who has a full complement of a liver, kidneys, and other potentially at-risk organs. Competing causes of cancer mortality or complementary risks from different cancer sites should be taken into consideration when presenting site-specific cancer slope factors.

c) Adequacy of the PBPK dose estimates for use to derive cancer slope factors should be discussed in each case. The Agency should investigate how far uncertainties identified during PBPK-modeling induce uncertainties on the cancer slope factors. The draft assessment should explain in more detail the differences between the Fisher (2000) model and the Clewell et al. (2000) PBPK models (see also the Panel response to Charge Question 6.) The discussion of those differences can then be related to Bois's (2000a,b) uncertainty analysis results.

d) The Agency should show how the conversion of TCA and DCA area under the curve metric between the chronic oral route and chronic inhalation route of exposure can be / has been performed (Section 4.2.3 of the draft assessment). Has there been a model applied? Which assumptions are used?

e) The set of cancer slope factors describing the range may be characterized by different uncertainties (sampling errors in the case of cancer slope factors derived from animal experiments, more complicated variability in the case of cancer slope factors derived from human studies) that should be addressed when presenting the range. Such characterizations are appropriate to help understand the role of the range of the cancer slope factors and prevent this range being naively interpreted as a range of high probability of the location of a true cancer slope factor.

f) The reader is not provided with an integrated treatment of comparable uncertainties for the different data inputs and routes to calculation. For the animal-based estimates, it appears that linear projections have been made from LED10s. Was some upper confidence limit calculated in the derivation of cancer potency factors from the human studies? Why should the statistical uncertainties built into the LED10s be treated differently from the uncertainty resulting from the use of different data sets, different estimates of exposure for the human studies, different pharmacokinetic models, or even different assumptions about the relevant dosimeter for particular endpoints? Sections 4.5.3-4.5.5 should be revised by taking those considerations and questions into account.

g) There is no weighting of the different bases (animal vs. human studies or cancer organ site) for estimating TCE cancer risks. Implicitly all values within the selected range are treated as equally likely, and there is no representation of the likelihood that the true population risk could lie outside the summary range provided.

### 7.2.1.3 Improved Mediation of the Cancer Slope Factors

For a better understanding of the role of the range of cancer slope factors for assessment of TCE risks and for using the range for guidance in deriving exposure limits in specific risk



AR100199

management problems, the strengths and limitations of this new approach should be discussed in the draft assessment. This discussion should address the following points:

a) The range is not an interval estimate in the sense of a statistical confidence interval and its concept is not grounded in a sampling model for populations. This reasoning provides actually another argument for not calculating a central tendency value (see also above, section 7.2.1.2 g).

b) The stability and robustness of the range as it is derived at present should be discussed in light of the perspective that a new study may appear exhibiting estimates at the lower or at the higher end of the current range. The sources of disturbance against which robustness is lacking should be explained in more detail, e.g., referring to the factors reflecting human variation, sensitive populations, and susceptibility, as specified in sections 1.6 and 3.3 of the draft assessment.

### 7.2.2. Further Studies to Be Included

The question posed to the Panel about the inclusion or exclusion of specific studies raised three issues.

a) The study of Hansen et al. (2001) should be included for the risk assessment of TCE and in particular for the derivation of cancer slope factors specific for the dose-response data available for this study. New valuable information for TCE cancer risk is expected for non-Hodgkin lymphomas, esophagus cancer and cervix cancer. The Panel also advises the Agency to review and consider the Pesch et al. study (2000) for inclusion.

b) Where epidemiological studies are the basis of risk estimates, EPA should review and consider all studies (positive and negative), and then make a separate determination about which studies to use to calculate the cancer slope factor.
These studies should be the ones, among the studies that are well designed, that would generate the most health-protective number. To select only studies with "statistically significant" results risks introducing a bias that good meta-analysis practice would avoid.

c) Exposures in most of the epidemiologic studies could be estimated. For example, the Hill Air Force Base study (Blair, 1998) did not report exposures in ppm, but there are monitoring data that would provide as accurate a guideline as using toxicologic data with a 10-20-fold adjustment.

### 7.2.3. Linear or Nonlinear Approach

The choice of a linear or a nonlinear approach for each tumor site is based on the mode(s) of action at that site. The Agency has clearly explained in the draft assessment the criteria for the choice of the linear or the nonlinear approach separately by tumor site. It has also described the key limitations of the nonlinear analyses, which are the uncertain identity of the active metabolites and the key events involved in TCE-induced cancers in humans and in animals. Whereas the linear approach represents a best estimate for the case where one believes the mode of action is direct or indirect interaction with DNA, and human inter-individual variability is not very large (see Hattis and Barlow, 1996), the nonlinear approach is used to quantify the extent of uncertainty and to incorporate this into the determination of RfD and RfC estimates.

The draft assessment does describe in Section 3.5 how the available data on mode of action would support either a linear or a nonlinear approach. However, the critical reasons for



AR100200

choosing the nonlinear extrapolation should be explained in more detail. The Panel advises EPA to provide the type of quantitative analysis supporting nonlinear modes of action that was included in some of the state-of-the-science papers (e.g., Bull, 2000)

The compilation of the cancer estimates in Figure 4-3 provides an excellent overview on the linear and nonlinear results as far as they were obtained from available data. The Panel also notes that nonlinear projections were made from LED10s for liver and testes.

There was disagreement on whether the database for TCE was sufficient to provide confidence in the risk estimates derived from nonlinear models. Ambiguities in the determination of the uncertainty factors in the nonlinear extrapolation complicate a comparison of risk estimates obtained by both methods (the linear and the nonlinear) for one tumor site.

### 7.2.4. Sensitive Populations

The Panel commends the Agency for providing the sections on sensitive populations and cumulative risks (pages 4-29, 4-30). It notes, however, that the draft assessment incorrectly suggests that the different slope factors apply to different characteristics of the exposed populations (page 4-30, lines 1-6). The Panel advises that Section 4.5.6.4 of the draft assessment be revised to indicate more clearly whether and how the various slope factors can be based on variability.

### 7.2.5. For Further Consideration

Finally, the Panel provides two suggestions that go beyond the present charge question, but are considered important for the refinement of the risk assessment of TCE.

a) Ultimately, EPA needs to use the TCE and other complicated cases to develop an integrated probabilistic methodology (e.g. using Bayesian methods) that will weight the different sources of information bearing on risks appropriately, fairly represent a fuller array of uncertainties, and systematically derive risk descriptors that are needed for different types of risk management analyses and decisions.

b) In this, it is important to provide both upper confidence limit estimates and the mean "expected value" estimate when developing risk ranges, to give users confidence intervals. It is also important to provide risk management guidance that might indicate when it is most appropriate to use mean values, or when to use high end values with confidence intervals. Arithmetic mean estimates may be particularly needed for use in juxtaposing costs and health benefits of different measures to reduce. Upper confidence limit estimates are needed for decisions under regulatory programs that seek to redistribute the burden of reducing uncertainty in risk on economic responsible parties who can make choices either to bring about risk reductions or fund research projects to reduce the persisting uncertainty of present risk estimates.



AR100201

# 8. CHARGE QUESTION 6

## 8.1. Agency Charge Question and Suggested Areas for Inquiry

Charge Question: Please comment on the use of calibrated models and uncertainty analysis to address the question of pharmacokinetic model uncertainty.

Suggested Areas for Inquiry: The calibrated models (Bois, EHP 2000a, 2000b) build on the pharmacokinetic models (Fisher, EHP 2000; Clewell et al, EHP 2000) by fitting them to additional datasets. Is the draft assessment's use of the calibrated models adequately discussed and supported? In addition, Bois's uncertainty analyses indicate the extent of uncertainty in the dose estimates calculated for the liver, lung, and kidney. Is the draft assessment's use of these uncertainty analyses to characterize pharmacokinetic uncertainty adequately discussed and supported?

## 8.2. Panel Response

The Agency is commended for including PBPK modeling and its uncertainty analysis into the risk assessment of TCE. In doing so, the Agency steps forward to meet recent requests that it use applicable methods for characterizing uncertainty in risk assessment. The Panel encourages EPA to proceed further in this direction and to include PBPK modeling into the risk assessment process with identification of the uncertainty in model structure and parameters.

Therefore, an uncertainty analysis should remain in the draft assessment. The Panel advises the Agency to show that uncertainty has been assessed on the best available scientific knowledge of the pharmacokinetics and pharmacodynamics of TCE. The use of an uncertainty analysis for the derivation of different dose metrics is useful for a more realistic dosimetry (the pharmacokinetic part) for the dose-response assessment. The Agency might, however, also explore formally including the pharmacodynamic elements in a more comprehensive uncertainty analysis (uncertainty of causal effect models).

The issue of uncertainty between the two models of Fisher (2000) and Clewell et al. (2000) is a natural evolution of a relatively new area. In this case, Dr. Bois's application of statistical methods (2000a,b) to estimate the level of uncertainty helped to strengthen the argument for application of PBPK modeling in this risk assessment process. Presently, there are at least 700 papers on PBPK modeling and the area is more than mature enough to be utilized by the Agency to meet its commitment in its cancer risk assessment guidelines to use biologically based modeling (USEPA 1999). In many ways, this risk assessment of TCE serves as a role model for the next generation of risk assessment from EPA.

The state-of-the-science papers on the uncertainty of PBPK models (Bois, 2000a,b) have been useful to aid in how to credibly apply the results of the Fisher and Clewell's pharmacokinetic models. Obviously, PBPK modeling should be accompanied by a realistic uncertainty analysis. However, one has to be aware that in the present case this is a multi-step approach based on assumptions and further uncertainties. The risk estimates and uncertainties reported in the draft assessment result after a three-step procedure extracted from the state-of-the science papers in the Environmental Health Protection Supplemental Volume of 2000, namely:

a) the basic but different Fisher (2000) and Clewell (2000) models

b) the Bois (2000a,b,) uncertainty analysis



AR100202

c) the use of the Bois (2000a,b,) results in the Rhomberg paper (2000).

Therefore, a transparent explanation of the model definition and the intended usage of the model output are crucial for understanding and applying the modeling and the model outcomes for the assessment of TCE. Substantially more explanation should appear in the revision of the draft assessment (using footnotes and/or appendices).

Specific issues related to modeling and uncertainty analysis that the Panel thinks are necessary for the clarification and the improvement of the Agency's draft assessment are explained below.

### 8.2.1. Modeling

Using pharmacokinetic models that estimate the target tissue dose for the key metabolites identified in the toxicity and carcinogenicity of TCE is an extremely useful tool. The Agency has recognized this by using these models in the draft assessment of TCE. Although these models in the assessment have their limitations in describing the complex pharmacokinetic reality, they are now evolving, perhaps to a point at which they can be used to identify experimental data to further verify the ability of the current models to predict levels of TCE and metabolites in the various target tissues.

As described in the draft assessment there are two PBPK models for TCE: one published by Fisher (2000) and one by Clewell et al., (2000). The basic structural differences between these models are briefly reviewed in the draft assessment (Section 4.2.1) but not the differences in estimation of key parameter values. Sources of the differences between the Fisher and Clewell models and their implications on the central estimates and on the output of the models and how they translate in dose and risk estimates should be provided. It is important to see how values are fed from one model into another. A critical evaluation of both these models with respect to structural features, assumptions, and parameter estimates needs to be included in this section prior to a discussion of the recalibration of these models by Bois (2000a,b). This discussion is necessary to understand the value and limits of each individual model as well as the parameter uncertainty associated with that model. The new discussion should explain the basic features of model building, prior information, new data, and posterior information of the calibrating models of Bois (see also a further discussion in section 8.2.2. of this report). It is also necessary to outline the differences between the simulations performed by Clewell et al. (2000) and the Bayesian hierarchical modeling of Bois (2000b).

The discussion should also seek to identify and describe the reasons why the Fisher and Clewell models seem to make divergent dosimetric predictions, and the likely sources of the residual differences between the model predictions after the Bois recalibration. The draft assessment mentions on page 4-3 that a Bayesian statistical framework and Markov-Chain Monte-Carlo (MCMC) simulation was used to refine the Fisher (2000) and Clewell et al. (2000) model by Bois (2000) using more data sets to estimate each model's parameters. It is also stated that the result is a set of calibrated models that better fits a wider range of experimental data. This discussion raised several issues in the Panel.

a) Bois (2000b) used the Clewell et al. (2000) model with three modifications: 1) one compartment was added to describe the gas uptake data from the work of Fisher et al. (see Bois 200b); 2) the volume of the poorly perfused compartment was changed; and 3) the computation of the blood flow to the richly perfused compartment was revised, but it is not clear in Bois (2000b) which PBPK parameter values were changed and why exactly those changes were made. It would be useful for the Agency to include in this section a discussion of the specific data sets



AR100203

that were used by Dr. Bois to update these models and how these specific data help in parameter estimation. In reviewing Bois's model (2000b) it appears that gas uptake data may have been the only new data set used for model calibration and estimation of variability and uncertainty. The Agency needs to include in the assessment a discussion concerning the limitations of only using gas uptake data for this purpose since they are an indirect measure of metabolism.

b) The characterization of the uncertainty and the use of PBPK models and their uncertainty analysis models should be fully described in the draft without requiring extensive consultation of the state-of-the-science papers in the EHP supplement issue (e.g., through an electronic appendix, including data and programs if available). Full documentation of the original data is recommended. The Panel also considers it important to identify which data were selected for the assessment of uncertainty, and which were not, and the rationale for the choices that were made in this respect.

c) Bois's modeling is a comprehensive modeling of all aspects of the pharmacokinetic modeling of derived dose metrics. Reproducibility of the methods used by Dr. Bois, however, is a question of concern. All assumptions going into the model should be made clear. The Panel asks that the models be made publicly available. If the assessment of TCE is based on the state-of-the science papers, it is necessary for the model to be available for independent researchers to reevaluate the analysis.

### 8.2.2. Uncertainty Analysis

Parameter uncertainty arises from many sources such as measurement errors or the use of surrogate data (indirect measurements of parameter values), as in the case of gas uptake data where changes in parent compound in a closed chamber are measured instead of observations of concentrations or generation rates of specific metabolites. Concern for parameter uncertainty should be discussed in this section of the assessment.

Model uncertainty arises due to gaps in understanding the specific mechanism(s) that affect both the kinetics and the dynamic actions of the compound in question. In Section 4.5.7.1, the draft assessment states that the full extent of model uncertainty cannot be quantified, only the models that have been analyzed This is an appropriate warning to the reader that the extent of model uncertainty that can be quantitatively assessed is limited by the analysts' creativity and the resources available for examination of alternative conceivable model structures consistent with available biological understanding. There appears to be model uncertainty with respect to the Fisher and Clewell models. The performances of different models with the same data sets can be compared on the basis of a common measure of goodness of fit. It is not made clear how the Bayesian method contributes to the analysis and how all the available information is used to judge the relative likelihoods that different models are right.

Several areas for improvement were identified. First, the type of uncertainty covered by the pharmacokinetic models of Bois (2000a,b) on the basis of the Fisher (2000) and the Clewell et al. (2000) models should be explained in much more detail within the draft assessment and in a way that enables the reader to assess the benefits and the limitations of these analyses (e.g., further explanation in terms of lack of knowledge and variation between individuals). The impact of all these modeling exercises on the dose estimates should be exhibited to a larger extent and discussed critically before using the specific modeling result [e.g., that of Bois (2000a,b)] to define the uncertainty and variability in the dose metric. The Panel advises that this be done before any dose metric is used for the derivation of cancer slope factors and the consequent uncertainty and variability in the cancer slope factors themselves.



AR100204

Another part of the model uncertainty that can be quantified concerns the differences in expected risks that are produced by assuming that one dose metric is the correct predictor of the risk of cancer at a particular site, relative to the risk produced by selecting another dosimeter. In particular, the impact of the uncertainty analyses on dose responses in humans should be addressed. Furthermore, median results taken only as dose estimates are not enough. It is necessary to use other percentiles of the distribution (or preferably a representative sampling of different outputs from the distributions of each plausible dosimeter) and define the effects on the distribution of risks.

The second area for improvement involves sources of uncertainty revealed by this modeling approach. These sources, assumptions about the parameter values and their variation, transfer of a number of parameter estimates between species, should be discussed and related to the gain in precision obtainable through this calibration. Skepticism about the posterior distribution, the comparability of the prior and the posterior parameters, and the sensitivity of the Bois model should be addressed by reviewing the weights that the Bois model places on the new calibrating information relative to the prior distributions. Prior information may not be given the weight it deserves or new calibrating information may be evaluated as having less uncertainty than it should.

The Panel notes several concerns related to the characterization of uncertainty.

a) In Section 4.5.7.1, the draft assessment states that the two pharmacokinetic models initially led to risk estimates that differed by 15-fold (see Table 4-4). It was stated that to reduce this uncertainty the models were fitted to additional data sets that improved the models and made them more compatible reducing model uncertainty. In reviewing Table 4-4 it is not at all clear what is being compared to get the 15-fold difference and how the calibrated models improve this. Also, based on what is presented throughout the draft assessment is it even appropriate to discuss DCA area under the curve as a dose metric? Notice that this clarification has a direct impact on the Summary and Conclusions section 1.5.1 on page I-9).

b) The information presented in Table 4.1 needs further explanation. At what dose levels of TCE were these dose metrics examined? A discussion (in Section 4.2.2) of the information content of the values in Table 4-1 and the appropriateness of the use of the span of the 95 % confidence interval would help judging the role of this approximate uncertainty analysis which has been used to choose dose metrics for the risk assessment.

c) For the benefit of research planning, uncertainty needs to be discussed separately for each metabolic or follow-up product and it should also account for the difficulties in obtaining experimental estimates of model parameters.

d) The difference of the pharmacokinetic models for male and females needs in-depth discussion. Is it intended to derive different estimates for male and females or is this difference just one aspect of population variation? Differences between males and females, if stated, should be explained also on the basis of the original data.

### 8.2.3. Data Availability

Questions have been raised on the cleanness or completeness of the data used in this modeling (e.g., DCA values reported to contain errors). It was also noted that Dr. Bois was given an early version of the Fisher model that was changed by the time the mice and human model reached publication (Fisher, 2000) and that there are new mouse and human data available from Dr. Fisher. This should be checked and if there are errors or unexplainable inconsistency, a



AR100205

re-analysis should be performed on order to get appropriately revised dose estimates, even if those errors were of minor influence on the final risk estimate. Therefore, it is strongly recommended to disclose the sources of the data which were used for this TCE risk assessment and to describe their availability. The full power of the Bois (2000a,b) modeling is obtained only if all available data are used.

### 8.2.4. Markov-Chain Monte Carlo (MCMC)

The section where the statistical analyses of the pharmacokinetic models are described (Section 4.2.1, 3rd paragraph) should be completely rewritten to describe very clearly and precisely the methods applied by Bois (2000a,b). Since this method has been discussed widely, the Panel advises the Agency to provide (e.g., in an appendix) a comprehensive summary of this methodology with a few key references. Without going too much into the details, the basic concept of the Bayesian hierarchical modeling should be outlined and the role of the MCMC method within the use of the Bayesian hierarchical modeling clarified, namely for the calculation of posterior distributions and the numerical integration necessary to achieve this calculation.



AR100206

# 9. CHARGE QUESTION 7

## 9.1. Agency Charge Question and Suggested Areas for Inquiry

Charge Question: Is it appropriate to consider background exposures and other characteristics of an exposed population as modulating the risk of TCE exposure in that population?

Suggested Areas for Inquiry: The draft assessment discusses the case that TCE's toxicity can be modulated by background exposures to TCE's metabolites. A modifying factor is proposed because the data for estimating the effect of co-exposures may not be available to risk assessors in the field, but the potential for modification of TCE's toxicity is present. How can the potential effects of co-exposure be best addressed?

## 9.2. Panel Response

The Panel is pleased that the Agency has taken the first steps of including the issue of cumulative risk in a health risk assessment. Although there was agreement that background exposures to TCE and/or metabolites is a very important issue, there was disagreement, as noted in section 6.2.3 of this report, about whether the RfD should be the method by which this background exposure is addressed.

In light of the prevalence of some ubiquitous background exposures in the general population, some panel members thought it prudent to apply a modifying factor to the RfD. This factor would address exposures shared by all and not simply due to site-specific scenarios best addressed by risk managers.

Other panel members argued against including an uncertainty factor for background exposure, because EPA is in the process of finalizing the cumulative risk assessment approach that provides a framework for taking background exposure into account separately from the derivation of the RfD. Since RfDs are often compared for priority setting, it is essential that a consistent approach to handling background be taken. In addition, total background exposures may best be taken into account through a thorough aggregate/cumulative exposure assessment for a specific scenario that needs to be addressed.

Another view noted that, unlike the RfD, the RfC was largely derived from human studies, and thus already incorporated these background exposures (because the study subjects likely had similar background exposures as the general population). Therefore, it was a reasonable argument for not applying the modifying factor.

If EPA decides to include an uncertainty factor for background, it will be helpful for EPA to include a rigorous discussion of the evidence that a cumulative effect is expected at human exposure levels based on the modes of actions proposed. Some members of the panel proposed that EPA utilize the available quantitative data and model the cumulative effect based on general background for human exposure levels.

The Panel agrees that regardless of EPA's final policy decision on whether or not to include an additional uncertainty factor in the RfD for background exposure, the Agency should detail more completely its reasons for choosing, or not choosing, such an uncertainty factor. Specific comments related to this issue follow.



AR100207

Humans are never exposed to only one agent in isolation. Particularly insofar as multiple exposures may share modes of action, common metabolic pathways, etc., it seems appropriate to consider background exposures of an exposed population as modulating the risk of TCE exposure. It is highly appropriate for EPA to consider background exposures to TCE's metabolites and to other compounds that produce the same metabolites, because the range of estimated adult doses for the general population for some of these compounds are comparable to or even exceed the range of estimated doses for TCE (Table 2-1 of the TCE draft assessment). For example, tetrachloroethylene, which produces the same metabolites as TCE, is present in the ambient air at levels 10 times higher than TCE. The same is true for the presence in water of the chlorination byproducts, DCA, and TCA, both of which are metabolites of TCE. DCA and TCA may be the active metabolites for some of the TCE's adverse effects, such as hepatomegaly and hepatic carcinogenesis. Thus, background exposures to these compounds clearly have relevance to the risk of exposure to TCE.

Understanding and measuring these background exposures presents many methodological issues. The human studies that state TCE is a primary exposure are still dealing with mixtures. For example, TCE was a primary exposure at Hill AFB but subjects were generally exposed to jet fuels such as JP- 4 (now JP-8) on a daily basis as well as other solvents besides TCE (LeMasters et al. 1997,1998; Stewart 1991). The Wilson et al. (1998) cardiac malformation study is a prime example of the challenge that this draft assessment faces with human studies having TCE as the primary exposure. In Section 3.4.5.1 of the draft assessment, it was reported that "women exposed to degreasing solvents, including TCE have reported elevated risks for cardiac anomalies in their offspring ...with an attributable risk of 4.6%" for hypoplastic left heart anomalies. The investigators, however, only asked the parents regarding their exposure to "solvents/degreasing compounds" but no specific mention of TCE was in the entire study. Further, it was not clear whether or not the mother or father was exposed, but what was known is that for 98% of the cases, the mother was interviewed and in 20% of the cases the father was present. In fact, generally it is unlikely the individuals know the exact compounds contained in degreasing or solvent exposure. This has been a common experience from interviewing numerous men and women at sites such as Air Forces Bases (see Hill AFB and articles by LeMasters et al., 1997, 1999). This suggests that based on the human studies, we cannot specifically implicate TCE, but can only use these studies as supportive evidence. The Agency needs a rigorous way of interpreting these studies and incorporating them into its assessment of background exposures.

In light of the prevalence of such exposures in the general population, some panel members thought it prudent to apply a modifying factor to the RfD, as is argued in Section 4.3.3 of the draft analysis. These panel members felt that in cases where data are available for estimating these co-exposures for all relevant populations, the modifying factor could be omitted. Some other panel members thought it reasonable not to apply the modifying factor to the RfC, and agreed with the Agency's argument that, unlike the RfD, the RfC was largely derived from human studies, and thus already incorporated these background exposures (because the study subjects likely had similar background exposures as the general population). It should also be noted that the cancer risk estimates based on animal data were not adjusted for background exposures. Yet another view was that the application of a modifying factor for background exposures was not appropriate.

The Panel feels that Tables 2-1 should include data on the estimated TCE metabolite levels derived from the TCE-related compounds. In particular, there is the need to estimate quantitatively how these background exposures would affect the risk of TCE. This should be used in a justification of a 3-fold factor (or some other factor) applied to the RfD for background and co-exposures.

Besides background levels of TCE, its metabolites, there are lifestyle exposures and other co-exposures that will theoretically modulate TCE metabolism, utilize the same metabolic pathways, or share targets of toxicity with TCE. Examples are acetaminophen and ethanol, which can theoretically alter susceptibility to TCE effects by influencing CYP2E1 activity. This leads to the recommendation that a table be developed providing a list of relevant exposures that modulate CYP2E1 with information that can be used to estimate the impact on TCE risk. In particular, this table should show how these exposures can be used to justify the choice of the 3-fold factor applied to the RfD.

Finally, the Panel feels that this important area of cumulative risk required more detailed treatment as it especially relates to TCE.



AR100209

# 10. CHARGE QUESTION 8

## 10.1. Agency Charge Question and Suggested Areas for Inquiry

Charge Question: Do the data support identifying risk factors that may be associated with increased risks from TCE exposure? Are there any risk factors that should/should not have been included?

Suggested Areas for Inquiry: Does the draft assessment adequately present and consider the data supporting identification of potentially susceptible populations, including the role of differences in enzyme activity to affect TCE's metabolism and toxicity?

## 10.2. Panel Response

Yes, the data support identifying numerous risk factors that may be associated with increased risks to susceptible subpopulations from TCE exposure. The EPA draft assessment has done a good job identifying the general areas of concern related to prenatal, reproductive, and developmental risks associated with TCE exposure, especially given the level of information known to date.

A major issue is related to multiple exposures and routes of exposure to susceptible groups from background exposures to ethanol, TCE and its metabolites, chemical solvent mixtures and the limited data available for perhaps the most susceptible population, the embryo/fetus, infant, and child, given the data found in Table 2-1. The Panel notes that that none of these exposures are voluntary to the fetus, newborn and infant. The implication of levels of exposure found in the ambient environment and relevance of exposure that might be found in breast milk, the fetal compartment or in other areas where infants are exposed such as with preparation of formula with TCE contaminated water supplies are basic areas of extrapolation. This approach could then serve as a long-term guide for future agents toward evaluating reproductive, prenatal, and childhood environmental exposures related to age specific effects. Numerous other potentially susceptible populations were identified and discussed, including individuals with underlying diseases that alter their metabolism of TCE, individuals on medications that alter CYP2E1, and individuals with diseases that put them at higher risk for developing kidney cancer, liver cancer, lymphoma, and other diseases. Concerns were expressed for diseased individuals (diabetes, hepatitis, HIV positive, etc.), who may be especially susceptible to TCE exposure. It is not clear whether their increased risk will fall within the 10-fold RfC population variability factor. Some further discussions on these potential high-risk individuals would be helpful.

The Panel advises the Agency to discuss other potential risk factors, including: reduced immune function in children and the elderly; genetic traits that result in variations in metabolizing genes; DNA repair genes; and inherited mutations in genes that predispose to particular diseases.



AR100210

# 11. CHARGE QUESTION 9

## 11.1. Agency Charge Question and Suggested Areas for Inquiry

Charge Question: Do the data support the possibility that TCE can affect children and adults differently? How can this be reflected in the quantitative assessment?

Suggested Areas for Inquiry: Given the potential for differences between children and adults, does the draft assessment develop toxicity values that are protective of children, including minimization of exposure through human milk? Does the draft assessment adequately consider the information on differences in metabolism and clearance between children and adults and appropriately characterize the potential for differences in response? With the data at hand, are there ways to make the characterization more quantitative? Does the TCE database warrant an explicit uncertainty factor to reflect data gaps concerning the potential risks to children?

## 11.2. Panel Response

### 11.2.1. Major Summary Consensus Points of the Panel

The Panel reached consensus on the following conclusions related to this charge question:

a) The data presented suggest that TCE can affect children differently than adults, although there is a very limited database of TCE in children due to lack of directly applicable studies. Based on the TCE database, children appear to be at greater risks than adults from TCE exposure, due to possible differences in exposure, metabolism, and clearance. In regard to end organ susceptibility, data from other solvents and neurotoxicants, in general, would indicate that the child's central nervous system function is potentially more susceptible to TCE than the adult.

b) The draft assessment does not explicitly discuss whether or not the uncertainty factors address risk to children or attempt to develop toxicity values that take children into consideration.

c) The Panel advises the Agency to provide a more complete discussion of the key articles and information relevant to the issue of differences between children and adults. The Panel recommends that there be a stand-alone comprehensive children's chapter that discusses all the children's issues, including exposure, susceptibility during pregnancy, pharmacokinetics, and pharmacodynamics, in addition to discussions of developmental animal and children data in every section.

The Panel advises the Agency to include in that chapter a discussion of the need for, or lack of need for, an additional quantitative children's uncertainty factor.

d) The Panel advises the Agency to support statements about differences between children and adults with a quantitative discussion, whenever possible. The Panel recognizes that assessment of children's end organ susceptibility will be one aspect especially difficult to quantify. The Agency could, however, examine developing uncertainty factors based on the known distributional estimates of quantitative differences in the pharmacokinetics, and pharmacodynamics of TCE and its metabolites in children of various ages as compared to adults (Ginsberg et al., 2002).



AR100211

In regard to the issue of an additional uncertainty factor for children, many members of the Panel feels that the data supporting the possibility that TCE can affect children differently than adults led to the conclusion that it would be prudent for EPA to add an additional uncertainty factor to protect children. They believed this additional factor was merited, based on heightened concern for children, given existing information, and also based on the uncertainty of the TCE risk assessment, given the limited developmental toxicity data available.

Others agreed that children are at possibly greater risk, but felt that the existing composite uncertainty factor of 3,000 for the RfD was already large and adequately protective of children. They suggested that a component of the "other uncertainty factor" (see section 6.2.3. of this Panel report) established to cover a wide range of uncertainties involving susceptibility and background could be explicitly identified as a children's uncertainty factor. Yet one other view was that the 50-fold human variability uncertainty factor for the RfD in the draft assessment was probably large enough that an additional factor for children was unnecessary. However, an additional uncertainty factor for children may be warranted for the RfC, which currently only includes a 10-fold factor for human variability.

Yet another view was that the discussion of children's uncertainty factor needed to be more closely linked to the critical endpoint under consideration. This view recommended the approach of Barton and Clewell. Based on the critical endpoint of concern, decisions could be made regarding whether or not there is residual concern regarding risks to children. According to this view, these decisions would then not be based on differences in exposure that will be routinely accounted for in the exposure assessment, but be based, instead, on pharmacodynamic concerns specific to children based on the endpoint of concern. For example, the decision might be different for liver-to-body weight changes than for neurologic effects, depending on the severity and nature of the effects.

The Panel's discussion of the issue of an additional children's uncertainty factor emphasizes the importance of the inter-relationships among various components of the Agency's risk assessment (again see section 6.2.3. of this report). It also underlines the importance of the Panel's advice that the Agency explicitly address the need for, or lack of need for, an additional quantitative uncertainty factor for children and clarify how that factor relates to other uncertainty factors used.

In regard to cancer and children's susceptibility, the Panel notes another issue concerning the complexity of the TCE assessment. The Panel notes that the issue of children's susceptibility is closely linked to the Agency's overall risk assessment approach. In response to Charge Questions 5 and 8, the Panel raises concerns about childhood leukemias and lymphomas associated with drinking water contamination (New Jersey Drinking Water Study). It should be noted that this is the only data set used by EPA to address children's cancer risk differently from adults. Thus, if EPA were to decide not to include that study in its determination of cancer risk, then an adjustment of the cancer slope factor would be needed to address the children's cancer risk issue.

### 11.2.2 Background to the Panel's Conclusions

The critical studies in the human population have not been completed. However, the pharmacokinetic and pharmacodynamic information that is available on TCE and its metabolites in children and developing animals present a strong case that the developing child may be more susceptible to adverse effects from TCE than adults. Until adequate data exist to determine the exact risk, the Panel advises the Agency to address explicitly how it will factor in protection for children into its quantitative risk assessment.

Generally accepted knowledge of the pharmacokinetics and pharmacodynamics of TCE, its metabolites (Fisher, 1989), solvents in general, and many xenobiotics support the overall conclusion that children, as compared to adults, are potentially at greater risk from TCE and its metabolites (Ginsberg, 2002; Hattis, 2002 in press; and Renwick 1998). If one takes an approach based on pharmacokinetics and pharmacodynamics, the embryo, fetus, infant, child, and adolescent (referred from here forward only as the "child"), as compared to the adult, have altered TCE exposure, absorption, metabolism, clearance, and potentially end organ susceptibility.

In regard to exposure and absorption, the Panel notes that the child is exposed to TCE and its metabolites transplacentally, via breast milk, and through the same routes as the adult. Since the infant has greater skin surface area by a factor of 2-3 on a per kilogram basis, they should absorb more TCE from the transcutaneous route than the adult. Transcutaneous absorption of TCE may also be increased in the human premature infant as compare to the adult due to increase permeability of the premature's skin as compared to the adult (Reed, 1996). Children drink more water and breathe more air than the adult, so exposure would be greater. Considering the large number of drinking supplies that have TCE, these exposure-related factors are of great concern for children (ATSDR, 1997. Fisher et al., 1989).

While there was agreement that differences in exposure assessment should be discussed more rigorously, including data that quantify these differences, there was no agreement on whether this difference in exposure should be the basis for additional uncertainty factors. Several panel members felt that the increased exposure of children to TCE can be determined and specifically factored in when the overall determination for human TCE uncertainty factors are calculated. This specific quantitative assessment and adjustment for TCE uncertainty factors due to children's increased exposure would then preclude additional nonquantitative assignment of uncertainty factors to be considered in the overall assignment of uncertainty factors of TCE.

In developmental biology, certain additional factors should be considered in risk assessment. One such factor is the fetal/maternal distribution of the chemicals. In one animal study (Ghantous et al., 1986), a TCE metabolite, TCA, appears to accumulate in the amniotic fluid after exposure of the mother to TCE. This accumulation may be due to several factors including fetal/maternal differences of protein binding, acid/base balance, or metabolism. The accumulation will result in higher body burdens in the fetus as compared to the mother.

The metabolism and clearance of TCE and its toxic metabolites have been examined by various studies (Fisher, 2000 and Clewell et al., 2000). Although there is no study that has addressed the clearance of TCE in children, general pharmacokinetic differences between children of various ages and adults have been explored by Ginsberg et al. (2002) and Hattis et al. (2002, In Press). Specifically, for pharmacokinetic parameters including elimination half-life, clearance, and volume of distribution, these workers assembled a database of human observations, principally from the pharmaceutical literature, and created a series of combined analyses from which reasonable assumptions about clearance of TCE by infants and children can be derived. This research is described in Appendix B to this report and the authors concluded that the clearance of TCE and metabolites are reduced in children, as compared to adults.

The Panel also notes that there is evidence that the clearance of many TCE metabolites, which are also toxic, is delayed. Delay of the clearance of chloral hydrate, TCA, TCOH (Mayers et al., 1991), and TCE-G (Gorecki et al 1990) have been reported. These reductions in clearance have resulted in the clinical recommendation that the prescribed drug, chloral hydrate not be used on a repetitive basis in the newborn due to delayed clearance of the choral hydrate and the metabolites (American Academy of Pediatrics Statement, 1993).

Also, from what is known from the metabolism of xenobiotics in the fetus and newborn, most of the major enzymes responsible for the metabolism of TCE and its metabolites are reduced in the fetus as compared to the adult (Tateishi et al., 1997). The reduced metabolism/clearance for many pathways continues through the newborn period and into infancy. Since the toxic effects of TCE and the metabolites are dose-dependent, the best indication is that TCE itself and chloral hydrate or TCOH are probably all toxic and have decreased clearance in the developing human, placing the child at increased risk. The metabolism of TCOH in the premature newborn has been shown to be decreased by as much as 5-fold (Mayers et al., 1991) and this compound is considered to be more toxic than some of the parent compounds. Some of the metabolites, such as TCA, were still increasing 164 hours after the single administration of chloral hydrate (Gorecki, 1991).

This decreased clearance is due to the decreased enzyme activity responsible for metabolism and clearance of TCE and the metabolites. As recently reviewed (Hattis 2002, Hines and McCarver 2002), the enzymes that are known to be greatly altered during human development would include at least the following important enzymes: P450 2E1, ADH, UDP-glucuronosyl transferases, GSTs, and P450 1A2 (fetus, newborn, and infant). The situation is even more complicated than just expression of specific enzymes in that select P450 and GST isozymes are present in the fetus and not to any great extent in the adult and visa versa. In addition, renal clearance of phase II products is decreased in the fetus and newborn. Finally, it is known that the enterohepatic circulation of glucuronidated substrates such as bilirubin is enhanced in the newborn resulting in increased body burdens of glucuronidated substrates excreted into the biliary tree.

Another major area of concern is TCE-related adverse effects. The Panel advises the Agency to consider the weight of evidence systematically, endpoint-by-endpoint and overall in regard to adverse effects of TCE and its metabolites on the developing fetus, infants, and children.

The Panel advises the Agency to discuss and assess studies of the cardiac teratogenicity of TCE and its TCE metabolites that are not included in the draft assessment (Fisher et al., 2001) as well as to review systematically the literature on cardiac teratogenicity (Johnson et al., 1998a, 1998b, Dawson et al., 1993).

Neurobehavioral toxicity also deserves more attention in the draft. The Panel notes, from animal studies of TCE and its metabolites, that the developing rodent may be more susceptible to altered neurobehavioral function. The Panel observes, however that a larger uncertainty factor for human variation was applied to the calculation of the RfD (50) than for the calculation of the RfC (10), even though the human data supportive of the RfC were based largely on central nervous system effects in healthy adults and did not address the potential greater sensitivity of children. The Panel advises the Agency to include in the draft assessment a structured evaluation of the literature concerning the neurotoxicological effects of TCE and its metabolites on children. Some specific suggestions for that discussion are included below.

The only developmental neurotoxicity study of TCE is the Taylor et al. (1985) study, which did not compare dosing during adulthood with gestational dosing and which did not report sufficient data to be able to determine a LOAEL in mg/kg. The authors describe neuropathological changes in the animals treated during development. Taylor (1985), looking at TCA, found the observed neurobehavioral effects may be permanent, if the exposure occurred throughout gestation and weaning, unlike other studies in adults where the effects appear transient. A study by Moser et al. (1999) reported that DCA produced neuromuscular toxicity including limb weakness and deficits in gait and righting reflex. Weanling rats were more

sensitive than adults. It is, however, unlikely that the levels of DCA associated with developmental neurotoxicity would be achieved with even very high exposures to TCE. Thus, there are not sufficient data to conclude definitely that the central nervous system of the developing organism is more sensitive to the effects of TCE than is the adult central nervous system. This is clearly an important research need.

There are no neurodevelopmental studies examining the offspring of children born to mothers exposed to TCE in the workplace. Also there are no neurobehavioral studies comparing children exposed to drinking water with different levels of TCE. These studies would be most difficult and expensive to conduct. Nevertheless, the Panel advises that the studies be conducted in order to assess the neurobehavioral risk TCE for children more accurately.

Due to the paucity of developmental, neurobehavioral, and neuropathological studies, it may be useful to look at studies of other chemicals and humans during development. In general, the finding that the developing mammal, including the human, is more susceptible during development to central nervous system toxic chemicals is generally well accepted. This is easily shown with ethanol in the Fetal Alcohol Syndrome seen in children exposed to ethyl alcohol in utero (Sood et al, 2001; Hannigan and Armant, 2000; Streissguth and O'Malley, 2000), and also with mercury intoxication (Marsh et al, 2001), and polychlorinated biphenyl exposure (Guo et al., 1996, Grandjean et al., 2001). The effects for example in Fetal Alcohol Syndrome are not only dramatic but also apparently life-long. TCE and its metabolites could almost be anticipated to cause greater harm in the child than the adult, and the harm may even cause permanent alteration in children

There are other toxicities of concern discussed in the draft assessment, such as birth defects (cardiac, eye, and central nervous system), endocrine disruption, hepatic toxicity, immune dysfunction, and cancer. In the human newborn, there has been some evidence that chloral hydrate is associated with hepatic dysfunction after a few weeks of exposure (Reimsche et al., 1989; Lambert et al., 1990). In regard to birth defects, there are animal and human population data that suggest that TCE and/or its metabolites may be associated with these birth defects. Studies in animals show some strong indications that TCE can cause birth defects (Dawson et al., 1993; Johnson et al., 1998a, 1998b). There are, however, some negative and ambiguous animal studies (Cosby and Dukelow, 1992; Fisher et al., 2001). There are also data from human studies that do not support the findings of specific birth defects, and in the studies that reported effects, some studies do not establish that the effects were due to TCE (Bove et al., 2000; Bove et al., 1995; Rodenbeck et al., 2000). The Panel advises the Agency to review and discuss this literature and to draw conclusions from it related to differential susceptibility of children.

An additional area of concern that has not been addressed in any developmental study is endocrine disruption. This is a potentially important area that may have significant impact.

All of these concerns demonstrate increased uncertainty and areas where more research is needed. In addition, more research is needed to determine whether toxicities to these organ systems occur in developing mammals at lower doses than in adults. The relevant questions concerning susceptibility are not only whether toxicities to these organ systems occur in developing mammals, but also whether they occur at lower doses than in adults and if the toxic effects are more severe and long lasting. The data on TCE are too limited to conclude either way, but the weight-of-evidence supports that the developing mammal may be at greater risk.

Another great area of concern is cumulative risk and in particular exposure to alcohol during gestation. The potential for chemical-to-chemical interaction between TCE and ethyl



AR100215

alcohol resulting in greater toxicity of both to the human fetus is substantial and should be carefully addressed in the draft assessment. This is particularly important as many human fetuses are exposed to TCE and alcohol.

In summary, the developing mammal, including the human, may be at greater risk from TCE than the adult. It would be a worthwhile effort to try to quantitate the potential differences observed in clearance, body burdens, and susceptibility. This task is very difficult to accomplish, since the clearance and toxicity of the TCE is different from the metabolites. Despite these difficulties it would be a worthwhile exercise.

### 11.2.3. How the Draft Assessment Can Be Improved

Overall, the review draft assessment is well prepared. The data on children are presented throughout the draft assessment. This is appropriate, but the overall review and understanding of the children's issues would be greatly improved if the overall pharmacokinetics and pharmacodynamics would be sequentially discussed in one section and the draft assessment included a comprehensive chapter on children.

A discussion of the various adverse outcomes (cancer, neurobehavioral dysfunction, cardiac anomalies, endocrine disruption and liver toxicity) and the potential mechanism of action need to be discussed for TCE and each of the metabolites. It is possible or even likely that there is not one mechanism of action, but many. It is possible that due to altered metabolism during development that the potential toxicity mechanisms may change.

It would be helpful for the Agency to discuss the pharmacokinetics and pharmacodynamics for each metabolite and the effects of each metabolite of TCE on the metabolism, clearance, adverse effects, and mode of action. The Panel advises the Agency to examine how age would alter the kinetics and dynamics and how TCE and the metabolites can interact with one another. There is a large amount of information for chloral hydrate that was not fully discussed.

The other issue is cumulative risk. A discussion of TCE's potential and probable interaction with maternal alcohol intake and other chemicals would be important and of high priority.

One area needing further clarification in the draft assessment is related to the timing of exposure to TCE during development. It is important to identify exposure scenarios through various routes and doses to the developing and growing fetus/child.). The Panel notes that mean exposure to TCE in the urban air is at about 0.3 ppb and water contamination is at 50 ug/L or less (Wu et al. 2000) and that Agency for Toxic Substances and Disease Registry estimates that up to one-third of drinking water supply sources have some TCE contamination (ATSDR, 1997) and advises the Agency to clarify if and how prenatal exposure to these levels is likely to be of concern. Further, what, if any, are the implications of fat storage during pregnancy and then mobilization of the fat during the last trimester? Exposures to the fetus and neonate, given these potential internal sources of exposure and given the considerable pharmacokinetic and pharmacodynamic uncertainty for children, need more detailed estimations. Breast milk exposure is of special concern, since TCE is lipophilic and is measured in breast milk. The question of a child's body burden, given these multiple exposures needs to be estimated and probably can be estimated fairly accurately. The footnote on page 1-15 of the draft assessment provides a critical example how the various scenarios could be developed showing the unit risk for water consumption.



AR100216

The uncertainty of the quantitative risk assessment is very high due to lack of data. Critical longitudinal studies after intrauterine and new born/infant exposure have not been done. Of particular concern are neurobehavioral effects, endocrine function, reproductive function, birth defects, and cancer. These studies will have to be completed in the human to improve the overall risk assessment for children. Regarding additional research needed, the Panel recommends that a study be done to evaluate the body burden of newborns and infants who are likely exposed due to air and/or water contamination. This may be accomplished via a combination of breath, urine, and possibly occasional blood sampling. Also studies addressing TCE interaction with other chemicals and in particular alcohol are important.

The key studies should be discussed at greater depth and length. Finally, when children's risks are discussed, the pharmacokinetics and pharmacodynamics of the parent compound and the metabolites for the pregnant female would improve the overall evaluation of the study.

In regard to cancer, the draft assessment would be improved with a discussion and examination of vinyl chloride exposure during development and cancer. In particular, the draft assessment might benefit with a comparison to potential TCE cancers in children, by comparing sensitivity and expression of the induced cancers.

One last comment regarding this and other EPA draft assessments, which state that children generally metabolize chemicals faster. This is not true in the fetus and is rarely true for the newborn and young infant (Hines and McCarver, 2002). A general statement should not be made. With the realization that the fetus may express different enzymes than the adult, the idea of just looking at expression of enzymes and not how they function in the metabolism of chemicals by the fetus may be too simplistic.



AR100217

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AR100220

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AR100225

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AR100226

# APPENDIX A
## SPECIFIC PANEL COMMENTS ON THE AGENCY'S ASSESSMENT OF NONCANCER ENDPOINTS

### 1. Specific Comments on Hazard Characterization for Noncancer Endpoints

This section considers whether the draft assessment adequately characterizes the data at each site of toxicity.

### 1.1. Liver Effects

This endpoint requires significant attention because the liver weight to body weight change (LW/BW) is the key endpoint used to establish the oral RfD. There are scientific data available on mode of action, species differences, case studies (both positive and negative) following oral ingestion, severity of effect, and the relationship between effect and duration of exposure that can greatly inform the selection of uncertainty factors. The Panel advises the Agency to include a critical evaluation of the key studies used for determining the oral RfD [e.g. Tucker et al., (1972), Buben and O'Flaherty (1985), Berman (1995)] in this section. It would be helpful to discuss the quantitative changes in LW/BW ratios and to determine if the National Toxicology Program (NTP) toxicology and carcinogenesis studies of TCE in four strains of rats (CAS No. 79-01-06) report any LW/BW changes either in the report or raw data base and how these changes relate to liver histopathology. Understanding how effects on LW/BW progress with increasing duration of exposure will provide a scientific basis for extrapolating from subchronic to chronic exposures.

The Agency's discussion of this endpoint refers to the state-of-the-science reviews by Bull (2000) and Barton and Clewell (2000) that summarize the effects of TCE, TCA, DCA and CH on increased liver size, but fails to also include the discussions on relevance of these findings to TCE toxicity based on the dose level and cytotoxicity. As discussed in the general comments, it would be helpful to accompany any discussion of metabolites, where possible, with a more quantitative critical evaluation of the data.

The Agency's discussion of this endpoint mentions the results of several animal studies that examined the hepatotoxicity of metabolites of TCE. Human studies that have examined hepatotoxicity associated with TCE metabolites or with compounds that have the same metabolites, such as PCE, should also be summarized and quantitatively analyzed here. An example is the study by Brodkin et al. (1995) that found significant hepatic ultrasound abnormalities in dry cleaning workers exposed to PCE, even in the absence of significant effects on routine liver function studies. Such a review should include a discussion of exposure levels.

Sub-section 3.4.2.2 of the draft assessment refers to Tier I, II, III studies, but the meaning of these terms is not explained until later in the text (footnote 46 to Section 3.6.2). The footnote should be moved to the first mention of the terms.

### 1.2. Kidney Effects

For TCE, the Agency notes that an RfD can be based on critical effects in the liver, kidney and developing fetus. There is very little information presented in the draft assessment (section 3.4.3.1) describing the kidney toxicity that was stated to occur in humans exposed to TCE and in rodents. There should be a more thorough summary of the human toxicity studies since some are negative and some report changes in urinary proteins reflective of damage. This



AR100227

does not come across in this draft assessment. It appears the RfD review was based on the kidney effects reported by Maltoni et al., (1986) where the specific effects in the kidney were not described in any detail in this draft assessment. Going back to this original study it appears that Sprague-Dawley rats were dosed orally for 52 weeks and then followed until natural death. The response of kidney meganucleocytosis was only observed in male rats at 250 mg/kg. It is not clear from what is presented in the Maltoni et al. publication or in the draft assessment whether this lesion is associated with normal aging or is thought to be a response to chemical exposure. There is a National Toxicology Program (NTP) report (1983: NTP TR 243) which reports karyomegaly of the renal tubular cells in male rats at 2000 mg/kg TCE and female rats at 1000 mg/kg TCE (13 week study). The Panel advises the Agency to reevaluate both of these studies and their findings prior to setting of the kidney NOAEL. It is also not clear why the Berman et al (1995) paper was not used by either Barton and Clewell or in the draft assessment to derive a LOAEL for kidney toxicity of 50 mg/kg/d with 14 day dosing. This would have lowered the human effective dose (HED) for nephrotoxicity and should therefore be explicitly addressed in the draft assessment.

### 1.3. Developmental Effects

The draft does discuss multiple effects on children and the developing fetus. The draft assessment discusses the evidence that TCE may be a cardiac (and possibly ophthalmologic) teratogen. This issue deserves greater attention and critical analysis. Cardiac teratogenesis has been reported in community-based epidemiological studies in which TCE was a contaminant. Four studies in the rat model (on TCE, TCA and DCA) have revealed significant excesses of cardiac defects. A relatively recent mechanistic study using chick embryos cultured on collagen gel (Boyer et al., 2000) has identified a possible mode of action by which TCE may cause cardiac defects – dose dependent inhibition of mesenchymal cell transformation. A more recent study by Fisher et al, (2001) failed to identify cardiac defects in the rat. Differences between this study and the other studies should be evaluated relative to sample size route of dosing, duration and timing of exposure, maternal toxicity, and relevance to humans.

The Panel advises the Agency to improve its discussion of the referenced studies and especially of the critical studies referenced in Table 4-2 for developmental toxicity (Narotsky et al., 1995a,b and Dawson et al,, 1993). The second paragraph superficially summarizes a number of positive developmental studies of TCE, TCA, and DCA without stating which study evaluated which compound. The studies that evaluated the developmental toxicity of TCE should be summarized and critiqued first. Data from the studies of the TCE metabolites, TCA and DCA, should be summarized separately and evaluated as to their consistency with the TCE studies and pharmacokinetics of TCE.

The Panel advises the Agency to discuss the strengths and weaknesses of the studies, based on dose-response relationships extrapolated to relevant occupational and environmental exposure levels, and based on relevance of methods used (e.g. chick embryos cultured on collagen gel; osmotic mini pumps delivering TCE directly to the uterine lumina). The section could by improved by discussing more several negative developmental studies that used inhalation exposure to TCE at relevant exposure levels. These studies are not referenced individually, but rather the reader is referred to Barton and Clewell (2000 ) [the actual referenced papers are Healy et al.(1982); Dorfmueller et al. (1979); and Hardin et al. (1981)]. These negative as well as the positive studies should be summarized and critically evaluated. Special attention should be given to the Fisher et al. (2001) paper that used 19-20 litters, high oral gavage doses, exposure duration of GD 6-15 which spans the critical periods of heart development in rats, and sensitive techniques conducted blind in collaboration with an investigator who initially detected an effect in an earlier study (Johnson et al., 1998).



AR100228

At times, the draft assessment makes overgeneralizations that make detailed and specific interpretations difficult. One specific example is in section 3.4.4.2. One study (Cohn et al., 1994) is reported related to childhood leukemia with an "observed very strong association" with exposure during pregnancy and an exposure response gradient with drinking water contamination as the etiologic agent with TCE "often the chemical found in highest concentration." Though the odds ratio is 13.2, the confidence interval includes 1 ranging from 0.9 to 205.2. Thus, the significance of this finding may be over-stated.

**1.4. Neurotoxicity Effects**

Several of the critical studies in Table 4-3 for neurotoxicity are human occupational studies. The Panel advises the Agency to discuss whether the subjects had other exposures besides TCE. For example, the study by Rasmussen et al. included workers with concomitant exposures to CFC113 as well as other unspecified solvents. The Arito et al. (1994) study was not discussed in Section 3.4.1. and should be discussed because it may be one of the most sensitive endpoints for setting RfCs based on neurotoxicity.

The text in section 3.4.1 refers to a study by Moser et al. from 1999 that used DCA as the test substance but does not discuss the dose-response relative to quantitative levels of DCA following TCE exposure to rats and to known relevant human exposure levels. This type of discussion is essential in order to understand the relevance of these studies to the TCE risk assessment. It is unlikely that DCA plays a role in TCE neurotoxicity, based on the discussions in the state-of-the-science papers (Lash et al., 2000; Barton and Clewell, 2000). The 1995 paper by Moser et al. that tested the neurobehavioral effects of 1- and 14-day exposures to TCE (referenced in Table 4.2), among other compounds, should be discussed in section 3.4.1. and included in the reference list. The Boyes et al. (2000) paper studying acute peak vs. repeated exposure, and the Moser et al. (1995) comparison of 1 and 14-day exposure should be evaluated in terms of providing information in extrapolation from shorter to longer duration exposures.

**1.5. Endocrine System Effects and Reproductive Toxicity Effects**

The relevant section of the draft assessment needs to be discussed more carefully because endocrine effects raise particular concerns for potential effects on the developing fetus, including concerns about vulnerable life stages that should be considered in the discussion about uncertainty factors and children's vulnerability. Therefore it is important that a more critical evaluation and balanced presentation of the data be given in this section. Additional specific comments on the human endocrine toxicity studies used in the derivation of the RfC are provided in section 2 of Appendix A of this report. Both negative and positive data should be reported including the results of the 2-generation reproductive studies with mice and rats using microencapsulated TCE in feed discussed in the state-of-the-science review by Barton and Clewell (2000).

In terms of reviewing the epidemiological literature, section 3.3.1.3 of the draft assessment reports excess risks of cervical cancer in occupationally or environmentally exposed women. More specific details of these studies are needed in order to bring clarity to the discussion, as specifics of the actual study findings are sparse. The report states "TCE exposure has been associated with excess risks of cervical cancer in occupationally or environmentally exposed women (Blair et al., 1998; Anttila, 1997; and Burg, 1997 cited). These studies typically cannot account for possible confounding from lifestyle factors. According to public comments provided to the Panel, the Anttila et al. (1995) study found a significant increase in cervical cancer for women exposed to TCE for less than ten years, but not for longer than 10. Blair showed non-significant but elevated breast cancer mortality rate ratios in the low level



AR100229

intermittent or continuous exposures (3.1-3.4) that were higher than those reported in those having frequent peaks RR=1.4. In the Blair et al. study (1998), cervical cancers had rate ratios of 1.8, which was not significant with confidence intervals of 0.5-6.5. Prostate cancers in men also were not significant. A more thorough description of the actual findings, limitations, and implications is needed.

In terms of male reproductive effects, the data are mixed. When evaluating cytotoxic effects of exposure to solvents and fuels containing TCA at Hill AFB, effects were observed related to an increase in micronuclei and sister chromatic exchanges (Lemasters, 1997, 1999a, 1999b). Although the epidemiological literature provides evidence for reproductive effects of TCE in men, but not in women, this is primarily because there are virtually no studies of reproductive function in TCE-exposed women. Thus, the human reproductive toxicity data cannot be used to determine whether TCE toxicity is modulated by gender.

In an NTP CD-1 mice study a 45% and 18% reduction in sperm motility was observed in the baseline and first generation of males, even though no effect was observed on mating, fertility, or reproductive performance. In contrast, the primary finding of the Zenick et al. 1984 study on male rats showed that TCE-related effects were seen primarily in the 1000 mg/kg group related to impaired copulatory behavior. The copulatory functions had returned to normal by the fifth week of exposure and essentially no effects on sperm parameters were observed. The conclusion from this latter study was that "TCE exerts minimal direct effects on the male reproductive system in terms of spermatotoxicity," but TCOH showed a 3-7 fold increase in the testis, prostrate, seminal vesicle, fat, liver, kidney and lung. The Zenick et al. study demonstrates the ability of the reproductive organs to concentrate TCE and its metabolites with increasing dose.

## 2. Specific Comments on Uncertainty Factors for NonCancer Endpoints

### 2.1. Human Variation

In the view of some panel members, the current draft assessment makes a potential error in treating the pharmacokinetic uncertainty as if it were a measure of human inter-individual variability. Some panel members nonetheless argued that EPA's choice of a 50-fold uncertainty factor could be justified on other grounds. These panel members felt that inter-individual variability in metabolism and response to TCE is likely to be large, especially when children are considered. The El-Masri (2000) analysis would appear to indicate that the data-derived factor for human variation and animal-to-human extrapolation combined should actually be 625x. EPA's analysis would be strengthened by explaining the range of data and methods available for assessing inter-individual variability and describing the rationale more clearly for the approach taken.

In addition, the 3.5-fold difference between adults and infants for metabolism of TCE should have been included in the EPA analysis. This could be addressed by specific modeling of human variability distributions (Renwick, 1998).

Pharmacodynamic variability is another matter. Different endpoints may be causally related to different metabolites and different dosimeters related to those metabolites [e.g. maximal concentration (Cmax) vs. area under the curve in relevant locations in the body]. Therefore, there may be different pharmacokinetic variability "uncertainty factors" for different endpoints. This would be a useful question for future research. A related issue concerns appropriate estimates of the pharmacokinetic portion of human inter-individual variability. The Panel encourages the Agency to explore deriving them by exercising the various



AR100230

pharmacokinetic models using the population variability of various pharmacokinetic parameters estimated by Dr. Bois, together with the dependencies (a more general word than "correlations") among the values of these parameters. Obtaining these inputs for variability simulations may require consultation with Dr. Bois. Variability should be calculated separately for different dosimiters putatively related to different adverse effects (e.g. areas under the curve vs. peak levels of key metabolites hypothesized to be involved in causing specific effects).

Ultimately, the whole system of uncertainty factors could be usefully revisited and defined in terms of an objective of achieving x level of risk for the yth percentile of the variable human population with z degree of confidence.

### 2.2. Animal-to-Human Uncertainty

In regard to the RfD, the Agency's RfD is based on effects on LW/BW ratio. The EPA document explores many different modes of action for TCE's effects on the liver. The state-of-the-science papers (Bull, 2000, Barton and Clewell, 2000) critically and quantitatively evaluate the likelihood of different modes of actions to be relevant. Barton and Clewell conclude that LW/BW alterations involve peroxisome proliferator-activated receptor (PPAR) and that the data do not support the standard default assumption that humans are more sensitive than the most sensitive rodents. The EPA document also acknowledges that humans in general have lower expression of PPAR alpha compared to mice and that these "quantitative differences have import to the dose response analysis of the mouse liver tumors (pp. 3-27). The EPA document should discuss this scientific evidence in their discussion of the selection of uncertainty factors. If different endpoints are used to derive temporary RfDs, as recommended by the EPA's SAB, then different considerations should be made depending on the most likely modes-of-action

In regard to the RfC, and in light of the supportive data for effects at similar exposure levels in the human studies, it seems appropriate to omit this factor.

### 2.3. Subchronic-to-Chronic Uncertainty

Regarding the RfD and RfC, some panel members felt that it was not appropriate to apply an uncertainty factor for sub-chronic to chronic effects to the "point of departure" dose because that dose was derived from chronic, as well as from subchronic, dosing studies. These panel members felt that EPA should not apply any uncertainty factors to composite "point of departure" doses, but should determine which uncertainty factors are scientifically justified for each of the critical studies. Then, these factors should be applied to the human equivalent dose for that particular study; the most protective value resulting from these calculations could then be chosen as the RfD or RfC.

It was unclear to some panelists why a full ten-fold factor was used for subchronic to chronic in the derivation of the RfC, but only a three-fold factor was used for the RfD. This point requires clarification in the draft assessment.

The liver endpoints bring up yet another issue, which is the definition of "chronic." Some panelists considered the 6-month study by Tucker et al. (1982) to be adequate to establish a chronic NOAEL. However, because the mouse lifespan is greater than 2 years, others felt that a subchronic-to-chronic uncertainty adjustment was needed, The Berman et al. study (1995) reported dose-dependent increases in liver weight after 14 days of dosing, and the Buben and O'Flaherty (1985) study after 6 weeks of dosing. One would like to be able to assess whether the effect was greater in the studies with longer dosing durations to support the use of an



AR100231

uncertainty factor for subchronic-to-chronic adjustment for the two shorter studies. Unfortunately, the Tucker et al. study did not report the liver weight values. Barton and Clewell (2000) argued that changes in relative liver weight are early events that are sensitive indicators of potential liver effects observed at later times, and therefore no adjustment should be made for exposure duration. This argument would be supported if there were no evidence of duration-response trends in liver weight or other aspects of liver toxicity.

The use of an uncertainty factor for sub-chronic to chronic dosing makes more sense for some of the endpoints than others. As the draft risk assessment points out, there is evidence for duration response trends for neurotoxicity from the human inhalation exposure studies. There are fewer effects from acute high exposures, compared to longer duration exposure [Moser (2000) and Boyes et al. (2000)]. The application of a subchronic-to-chronic uncertainty factor to developmental toxicity studies, such as Dawson et al. (1993) and Narotsky et al. (1995) does not make sense from a scientific point of view, because pregnancy is not a chronic state. The application of uncertainty factors is somewhat endpoint-specific and combining uncertainties from different endpoints may be difficult to justify scientifically.

In regard to the RfC, the Panel notes that the RfC includes a 10-fold factor for subchronic-to-chronic. However, it could be argued that the critical human studies cited in Table 4-3 of the draft assessment as being of "subchronic" duration should be considered chronic studies because the mean exposure durations ranged from 5 to 16 years. The draft assessment should explain how this might impact such a factor. The Arito et al. neurotoxicity study was a 6-week study. Some panelists said that if duration-response effects were observed in the supportive human neurotoxicity studies, it seems appropriate to apply this factor to this study. For the liver weight effects observed in the 30 day Kjellstrand (1983) study similar arguments can be made as for the liver effects in the oral dosing studies. Applying this factor should depend on whether there is any evidence of duration-response trends for this endpoint. Other panelists supported the use of a ten-fold factor for subchronic-to-chronic and urged the Agency to also apply the full ten-fold factor to the RfD.

### 2.4. LOAEL-to-NOAEL Uncertainty

In regard to presentation and communication of the Agency's justification for choosing NOAELs and LOAELs for the RfD, Table 4-2 needs to explicitly identify which NOAEL/LOAEL goes with which effect. In Table 4-2, first row, the NOAEL of 18 mg/kg/d for males seems to be from the Tucker et al. (1982) study for liver weight, not the Sanders et al. (1982) study as indicated in the table. In contrast, the 18-mg/kg/d dose represents a LOAEL for cell-mediated immune response to sheep erythrocytes in females from the Sanders et al. study. The 217 mg/kg/d NOAEL in males is identified as coming from the Sanders et al. study, and seems to refer to the humoral response to sheep erythrocytes after 6 months of TCE exposure. Other effects were seen in males at lower doses, and it is not clear why those were not chosen as the critical effect. For example, the recruitment of peritoneal cells showed a dose-dependent decline with a LOAEL of 18 mg/kg/d in males at 4 months. For several of the other parameters, there was not a clear dose-response in males. The female NOAEL/LOAEL of 193 mg/kg/day could not be found in either of those studies of 193 mg/kg/d. The NOAEL for liver weight in females in the Tucker et al. (1982) study was 437 mg/kg/d according to the text. Tables 3 and 4 from Barton and Clewell (2000), which is referenced as a source of the experimental doses listed in Table 4-2 of the TCE draft assessment, identify a NOAEL for immunotoxicity from the Sanders et al. study as 200 mg/kg/d. This is because they discount the LOAEL of 18 mg/kg/d in females for the cell-mediated response to Sheep Red Blood Cells and in male for peritoneal macrophage recruitment. Barton and Clewell cite the difference between the naïve and vehicle controls for the former and do not mention the latter. Regarding the effect on peritoneal



AR100232

macrophage recruitment, Sanders et al. state that the vehicle control levels in the males were higher than their historical controls, so that may be the reason for not considering that a critical effect.

Use of the statistically significant effects that were observed in the Sanders et al. study at 18 mg/kg/d as the critical effects would have resulted in a HED NOAEL for immune effects of less than 1 mg/kg/d, so this is an important issue.

In Table 4-2, row 3, the 50-mg/kg/d dose is a LOAEL for liver weight and kidney weight according to Table 4 of the original Berman et al. (1995) paper. The text and Table 3 of the Berman paper list 150mg/kg/d as the LOAEL in the multivariate ANOVA, which included serum liver function test values and liver histopathology, as well as liver weight. Barton and Clewell (2000) considered 50 mg/kg/d to be a LOAEL for liver toxicity in the Berman et al. study. It is not clear why the Berman et al. paper was not used by either Barton and Clewell or in the draft assessment to derive a LOAEL for kidney toxicity of 50 mg/kg/d with 14 day dosing. This would have lowered the HED for nephrotoxicity and should therefore be explicitly addressed in the draft assessment. The Maltoni et al. study (1986) from which the HED in Table 4-2 is derived dosed male Sprague-Dawley rats for 52 weeks and then followed the animals until their natural deaths, so some recovery from nephrotoxicity might have occurred before the kidneys were evaluated. In the Berman et al. study, female Fisher 344 rats were dosed for 14 days and the kidneys were evaluated the 24th day after the last dose. Thus there were sex, strain, and experimental differences between the two studies.

In Table 4-2, row 3, the 150 mg/kg/d dose is a NOAEL for neurotoxicity following 14d of exposure by gavage (Moser et al., 1995). Interestingly, the neurotoxicity of DCA, a metabolite of TCE, was found in another study by Moser et al. (1999) to be significantly greater by the drinking water than the gavage route, to be duration-dependent, and to be greater when dosing was started at weaning than in adulthood. Although the latter study tested DCA rather than TCE, it raises considerable uncertainty about the extrapolatability of the 150-mg/kg/d neurotoxicity NOAEL to chronic situations, to susceptible subpopulations (the young), or to drinking water exposure (the more relevant route in humans). The observation that, for chronic oral dosing with DCA, bolus administration of the entire daily dose by gavage results in less toxicity than gradual administration of the same dose over the 24 hour period in the drinking water suggests that one should not assume that gavage dosing with TCE is equivalent to dosing via the drinking water. This suggests a research need for direct comparison of the effects of gavage and drinking water dosing with TCE on various critical endpoints.

The discussion above points out additional issues that EPA may need to consider. However, the final decision on selection of endpoints should be based on the weight-of-evidence and consistency of findings across well-conducted studies. For example, the Berman et al. study was a research study designed to develop screening methods and used 8-animals/dose group and exposure was only 14 days. Certain endpoints measured in this study may have been better evaluated in other more robust subchronic studies. Careful critical evaluation of the strengths and weaknesses of studies is essential in the selection of key studies and critical endpoints. As mentioned in general comments, tabulation of studies will go a long way towards making the EPA's decisions transparent and help the EPA identify areas that require further discussion in the text.

In regard to presentation and communication of the Agency's justification for choosing NOAELs and LOAELs for the RfC, in Table 4-3, row 2 of the draft assessment, the 30 ppm LOAEL is given as the mean time-weighted average exposure for the workers in the Chia et al. (1997) and Goh et al. (1998) study and the mean exposure duration is stated to be 5 years. The



AR100233

30-ppm figure was obtained by personal breathing zone monitoring on 12 of 85 individuals who participated in the study. There is no indication given in the articles as to whether it is reasonable to assume that exposure levels in the factory had not changed significantly over the past 5 years. This would be important to know to assess whether it is appropriate to use the 30-ppm level as the mean chronic exposure level. The articles also do not mention whether the workers had any other concomitant exposures. It is also not clear why the authors chose to use analysis of variance, with years of TCE exposure as a categorical variable, rather than linear regression, with years of TCE exposure as a continuous variable, as the method of analysis. In fact, the categories into which TCE exposure duration is grouped are different in the two papers even though the data are the same. Another shortcoming is the absence of an unexposed control group. Despite these shortcomings, the authors did find significant relationships between some serum hormone concentrations and years of exposure to TCE using analysis of covariance with adjustment for age, smoking, and testicular size. There were significant inverse relationships between TCE duration and serum FSH, sex hormone binding globulin, and insulin levels. There was a significant positive relationship between dehydroepiandrosterone (DHEAS) levels and TCE duration. There was also a significant negative correlation between years of TCE exposure and testosterone levels, but this relationship became non-significant after adjustment for age, smoking, and testis size. The argument can be made that the authors should not have adjusted for age or testes size because neither one meets the criteria for a potential confounding variable of being significantly associated with the exposure variable and the outcome variable. Age clearly is a surrogate for years of TCE exposure in that older workers are likely to have more years of exposure. Although testosterone levels tend to decrease with age, this is typically not observed until after the age of 50. In this young cohort it is very unlikely that the significant negative correlation observed between age and testosterone levels represents the effect of age on testosterone. It is more likely that age is acting as a surrogate for exposure and, thus, that adjusting for age will falsely reduce the relationship of interest (i.e., the relationship between exposure and testosterone). For testes size, there is no reason to believe that this variable would be independently associated with exposure, and therefore, it does not make sense to adjust for it.

The LOAEL of 40-60 mg/L urinary TCA (20 ppm TCE) listed in Table 4-3, row 5 for the Rasmussen et al. (1993) study is better justified than the LOAEL in the Chia (1996,1997) and Goh (1998) papers. The authors use historical exposure monitoring data from the Danish Labor Inspection Service for the period 1947-87 to establish that this was the typical TCE exposure range during that historical period. One flaw of the exposure assessment of this study is that a significant subset of the subjects (25 of 99) were primarily exposed to CFC 113 rather than TCE, but these two groups were lumped together in the calculation of the cumulative solvent-exposure index. Nonetheless, there is a convincing dose-response relationship between increasing solvent exposure and number of abnormal coordination tests.

Although the LOAELs for the human neurotoxicity and endocrine toxicity studies have a good bit of uncertainty associated with them, as illustrated by the above discussions, the estimated HED LOAELs from 5 different human studies fall within a remarkably narrow range (7-16 ppm). Additional confidence in using these levels as the point of departure is provided by the subchronic rat neurotoxicity study by Arito et al. (1994) from which a HED LOAEL of 9 ppm was derived, and the LOAEL of 12 ppm for liver toxicity in the subchronic mouse study by Kjellstrand et al. (1983). It may be more appropriate to use the animal studies as the critical studies, with the other human studies as supportive studies. This is mainly because none of the human studies had long-term exposure data on the individual level. The study by Ruitjen et al. (1991) had the best exposure information (area samples from the plant spanning several decades and specific information about when changes such as installation of exhaust ventilation occurred) and chronic exposure indices based on the monitoring data were calculated for each subject. The Vandervort and Pelakoff (1973) and Okawa and Bodner (1973) studies were



AR100234

National Institute for Occupational Safety and Health (NIOSH) Health Hazard Evaluations that had good current exposure data in the form of personal air samples and urinary TCA. Both studies lacked information about chronic exposure conditions, and the Okawa study lacked a control group or any analysis of an exposure effect relationship.

In regard to the Agency's choice of NOAELs and LOAELs for the RfD, the Panel does not agree on whether an uncertainty factor for duration is needed, given that the LW/BW is considered more of an early event in the toxicity process and a sensitive indicator of potential liver effects observed at later times. The sizes of the changes are small (12 % -7%) (see Barton and Clewell, 2000). Other panelists supported the use of a ten-fold uncertainty factor. Several panelists questioned why EPA uses a full ten-fold uncertainty factor in the derivation of the RfC, but decreases the factor to only three-fold for the RfD. The Panel suggests that EPA clarify this issue in the draft assessment.

Another view cautioned EPA in treating the LED10, derived from a benchmark dose analysis, as a LOAEL. The original basis for the selection of LED10 is that it most closely estimated NOAELs for large numbers of developmental studies (Allen, 1994). Some panelists believed the benchmark dose should be reducing uncertainty, not requiring more uncertainty to be added. Other panelists argued that the LED10 is by definition an effect level and that therefore it more closely approximates a LOAEL. The benchmark dose approach is considered a more preferred approach to estimate the point of departure that takes into account the experimental variability.

In regard to the Agency's choice of NOAELs and LOAELs for the RfC, Barton and Clewell argued that the LOAEL of the Arito et al. (1994) study reflected a minimal, though statistically significant effect, and should be evaluated to determine if clinically significant effects were seen at the lowest dose level. Therefore, the application of a 10-fold uncertainty factor for LOAEL to NOAEL extrapolation is justified if effects are noted in the Arito et al. neurotoxicity study and are consistent with the weight-of-evidence from other carefully conducted neurotoxicity studies. The Kjellstrand et al. (1983) study also identified a LOAEL (for liver weight), and the application of an additional factor may be justified depending on the duration-response trends for this endpoint. On the other hand, some panelists suggested that if the benchmark dose (derived by Barton and Clewell) is used, then an uncertainty factor should not be automatically applied. There was a question in the minds of some panelists about why only a three-fold uncertainty factor is used for the LOAEL to NOAEL extrapolation in the derivation of the RfD, when a ten-fold factor is used here. They suggested that the Agency improve the consistency of the draft assessment by applying a standard ten-fold factor throughout. Other panelists disagreed and felt that the use of different uncertainty factors for the RfD and RfC could be appropriate if justified by the scientific evidence.

### 2.5. Other Factors

Some panelists believed that use of medications and presence of diseases is part of the default human variability factors and should not be double counted, while others pointed out that these might further extend the range of variability and would require an additional uncertainty factor. The Panel advises EPA to consider a point raised by Dr. Clewell in his public comments submitted to the Agency, namely, that induction of CYP2E1 is not likely to have a major impact on increasing oxidative metabolism at environmentally relevant concentrations of TCE. This argument may or may not be correct and would be a good topic for future research



AR100235

# APPENDIX B
## RECENT RESEARCH ON GENERAL PHARMACOKINETIC DIFFERENCES BETWEEN CHILDREN OF VARIOUS AGES AND ADULTS

General pharmacokinetic differences between children of various ages and adults have been explored by Ginsberg et al. (2002) and Hattis et al. (2002, in press). Specifically, for pharmacokinetic parameters including elimination half-life, clearance, and volume of distribution, these workers assembled a database of human observations, principally from the pharmaceutical literature, and created a series of combined analyses combined analyses using a regression-type approach. This analytical technique allowed them to bring data from many different chemicals together to assess geometric mean ratios of the values seen for children of particular ages in relation to adults.

Table 2 shows antilog (geometric mean) results from this type of analysis for elimination half lives, together with ± 1 standard error uncertainty ranges, for the database as a whole, and for drugs sorted by their major elimination. As indicated by the examples in Table 2, dividing the database into subsets according to either pharmacokinetic processing categories or pharmacodynamic modes of actions can allow inferences to be made about different age-related dosimetric adjustment factors that may be applied for members of those groupings. Using this same framework, analyses were also made of the distribution of residuals from the models—yielding an indication of how often the results for individual chemicals would be expected to differ by various amounts from the geometric mean within each group.

It can be seen in Table 2 that overall premature infants show about a 4-fold prolongation of elimination half life; and infants under 2 months of age have about double the half life of adults. The 6-month to 2-year age group shows, if anything, a slightly shorter geometric mean half life than in comparable adult studies. The departures of individual findings from these overall tendency tend to show much greater inter-individual pharmacokinetic variability in the time periods from 1 week to 2 months when the switch from early infant patterns of metabolism to more mature patterns takes place (Hattis et al., 2002 in press).

Based on these data, one can suspect: a) greater internal exposure per unit external exposure to unchanged trichloroethylene in the youngest infants; b) greater persistence of any activated metabolites that are generated in the youngest infants (although the rates of generation may be slower); and c) perhaps some more rapid metabolism and generation of activated intermediates per unit of external exposure for babies in the 2-6 month age range. More definite conclusions would of course require more specific data on the patterns of age-related changes in the several activation vs detoxification steps that trichloroethylene undergoes in people. No specific data are available at present about developmental changes in the rates of generation of the glutathione-transferase metabolites, the balance between glutathione and P450-metabolic intermediates, or the rates of elimination of the activated metabolites generated by these two competing pathways.



AR100236

**Table 2. Geometric Mean Ratios of Child/Adult Elimination Half-Lives.**[6]

| Major Elimination | Premature | Full term | 1 wk - 2 | 2 - 6 mo | 6 mo - 2 yr | 2 -12 yr | 12 - 18 yr |
|---|---|---|---|---|---|---|---|
| All pathways | 3.89 | 1.96 | 1.93 | 1.17 | 0.79 | 0.98 | 1.11 |
| All CYP (P450 | 4.52 | 1.83 | 3.51 | 1.22 | 0.51 | 0.61 | 0.73 |
| All Non-CYP | 3.43 | 1.80 | 1.46 | 1.06 | 0.98 | 0.92 | 1.11 |
| Unclassified | | | | | 1.00 | 0.94 | |
| **More detailed classification:** | | | | | | | |
| CYP1A2 | 2.74 | 9.45 | 4.29 | 1.24 | 0.57 | 0.54 | |
| Renal | | 2.78 | 2.75 | 1.15 | 0.81 | 0.60 | 1.13 |
| Glucuronidation | 4.40 | 2.98 | 2.15 | 0.98 | 1.19 | 1.36 | 1.47 |
| CYP3A | 5.28 | 2.08 | 1.91 | | 0.41 | 0.61 | 0.73 |
| CYP2C9 | | 2.19 | | | 0.55 | 0.77 | |
| Other, mixed CYP's | | 1.27 | | | | 1.08 | |
| Other Non-CYP's (not | 0.41 | 1.22 | 1.05 | 0.77 | | 1.24 | 1.41 |

[a] Parentheses show the ± 1 standard error range.

[6] Data represent regression results from 135 data groups for 41 drugs, Log(Arithmetic Mean Half-Life) Data. Please consult Hattis et al. (2002) for information about the equation fit.



AR100237

# APPENDIX C

**Biosketches of Members of the US EPA Science Advisory Board (SAB) Trichloroethylene Health Risk Assessment: Synthesis and Characterization Review Panel (TCE Review Panel).**

**Anderson, Henry: Wisconsin Division of Public Health, Proposed Chair of the TCE Review Panel and Current Chair of the SAB's Environmental Health Committee. Also a current member of the SAB Executive Committee.**

In 1980 Dr. Anderson joined the Wisconsin Department of Health and Social Services as the State Environmental and Occupational Disease Epidemiologist. In 1991 he also assumed the duties of Chief Medical Officer. Among his duties for the State of Wisconsin has been the development of the scientific support draft assessments for Wisconsin's Groundwater Enforcement Standards. One standard promulgated was for TCE. He was also responsible for state fact sheets on TCE in air and at hazardous waste sites.

He received his MD degree in 1972 and entered an Internal Medicine internship and then an occupational medicine residency. He was certified in 1977 by the American Board of Preventive Medicine with a sub-specialty in occupational and environmental medicine and in 1983 became a fellow of the American College of Epidemiology. He holds adjunct Professorships at the University of Wisconsin - Madison, Department of Preventive Medicine and the University of Wisconsin Institute for Environmental Studies, Center for Human Studies. He has published over 160 scientific articles on a broad spectrum of environmental, occupational and public health topics. He is principal investigator on nine active grants and cooperative agreements from federal government agencies including the U.S. EPA. None of these focus upon TCE, although the ATSDR Superfund Site Assessment Cooperative Agreement has evaluated sites contaminated with TCE and conducted exposure assessments.

His US EPA funded research grants address children's health issues, such as reproductive and endocrine function of frequent Great Lakes sport fish consumers and evaluation of women's awareness of mercury toxicity and sport fish consumption advisories. Other current research includes, childhood asthma, lead poisoning, arsenic in drinking water, youth occupational health, occupational fatalities and bioterrorism response. His expertise includes public health, preventive, environmental and occupational medicine, respiratory diseases, epidemiology, human health risk assessment and risk communication.

He was a founding member of the Agency for Toxic Substances and Disease Registry (ATSDR) Board of Scientific Councilors (1988-1992). He served on National Academy of Sciences/Institute of Medicine (NAS/IOM) committees that developed the reports "Injury in America" and "Nursing, Health & Environment." He was a member of the Armed Forces Epidemiology Board. He is current chair of the Environmental Health Committee of the USEPA Science Advisory Board and past chair of the SAB Integrated Human Exposures Committee. He serves on the USEPA SAB Executive Committee. He serves on several other FACA committees including the Director's Advisory Board for the National Center for Environmental Health, Centers for Disease Control and Prevention, the Hanford Health Effects Subcommittee for ATSDR and is a member of the NIOSH Advisory Board on Radiation and Worker Health. He is a fellow of the Collegium Ramazzini and the American Association for the Advancement of Science. He is associate editor of the American Journal of Industrial Medicine and serves on the editorial board of Cancer Prevention International.



AR100238

**Blair, Aaron: National Cancer Institute, National Institute of Health**

Dr. Blair is Chief of the Occupational Epidemiology Branch of the Division of Cancer Epidemiology and Genetics, National Cancer Institute. His research has focused on cancer risks from agricultural exposures, industrial chemicals, physical inactivity, occupational exposures among women, and methodolologic issues in occupational epidemiology. He has over 250 publications. He has evaluated the risk of non-Hodgkin's lymphoma, leukemia, and multiple myeloma among farmers in the first case-control studies to obtain detailed information on pesticide used and application practices. This work has culminated the development of the Agricultural Health Study, a long-term prospective study of 90,000 farmers and their spouses in Iowa and North Carolina. His studies of cancer mortality among workers exposed to the important industrial chemicals formaldehyde and acrylonitrile were among the first to employ sophisticated algorithms to develop quantitative estimates of exposure in multi-company studies. He has evaluated cancer risks among women in studies of dry cleaners and aircraft maintenance workers, who have significant exposures to various organic solvents including tetrachloroethylene and trichloroethylene. Methodologic studies have focused on confounding, meta-analysis, and misclassification in exposure assessment.

Dr. Blair has served on: IARC Monograph Working Groups; Environmental Protection Science Advisory Panel Subgroup on Atrazine; Federal Panel on Formaldehyde; National Center for Toxicologic Research Consensus Conference on Formaldehyde; IARC Workshop on Priorities for Epidemiologic Studies on Occupational Cancer; Advisory Committee to Trans-Canadian Study of Lymphatic and Hematopoietic Cancers; Task Force on Environmental Cancer and Heart and Lung Disease; Advisory Panel to Bureau of Chronic Disease, Health and Welfare, Canada on Future Research Directions; Farmers Study Advisory Committee, Health and Welfare, Canada; Advisory Group for Canadian Environmental Health Survey, Health and Welfare, Canada; NIH Inter-Institute Breast Cancer Working Group; Science Advisory Committee for the Lower Mississippi River Interagency Cancer Study; Louisiana State University Medical School; DHHS Environmental Health Policy Committee Subcommittee of Data Needs; Expert Panel on Domestic Use of Pesticides, National Cancer Institute of Canada; NCI Program Review Group on Leukemia, Lymphoma, and Multiple Myeloma; Cancer Research Methods Team; National Occupational Research Agenda, NIOSH; NCI Intramural Advisory Board; National Toxicology Board of Scientific Counselors; and on Organizing Committees for Conferences on Assessment of Smoking in Occupational Studies, Exposure Assessment in Occupational Investigations, and Physical Activity and Cancer.

He has served on Editorial Boards of the American Journal of Epidemiology, Scandinavian Journal of Work, Environment and Health, and the Journal of Agricultural Safety and Health. Dr. Blair is a member of the American Epidemiologic Society and a Fellow and Board Member of the American College of Epidemiology.

Academic Degrees: B.A., Kansas Wesleyan University 1965 Biology; M.S. North Carolina State University, 1967, Botany; Ph.D .North Carolina State University, 1970, Genetics; M.P.H., University of North Carolina, 1976, Epidemiology.

**Borghoff, Susan J.: CIIT Centers for Health Research**

Dr. Susan Borghoff has been a Staff Scientist at CIIT Centers for Health Research in the Research Triangle Park, North Carolina since 1989 following her postdoctoral fellowship. Prior to her position at CIIT, Dr. Borghoff was a graduate student at the University of North Carolina and conducted her research at the National Institute for Environmental Health Sciences (NIEHS).

Along with Dr. Borghoff's research program at CIIT she is also the Director of Education Programs which involves oversight of the pre- to post- graduate training programs and K-12 educational outreach activities. Her research interests have focused on understanding the mode-



AR100239

of-action by which specific chemicals cause kidney toxicity and cancer in rats with a view to understanding the relevance of this response for human risk assessment. Her research has also focused on understanding the metabolism and pharmacokinetics of various chemicals with emphasis on the development of physiologically based pharmacokinetic models that can be used for risk assessment.

Currently Dr. Borghoff's research is focused on the developmental pharmacokinetics of estrogen-like compounds such as genistein. CIIT Centers for Health Research is a not-for-profit research institution in which the major core funding is a grant from the American Chemistry Council Long-Range Research Initiative. Other financial support comes from government agencies (U.S. Environmental Protection Agency (USEPA) and NIEHS), independent research organizations, trade associations, and corporations. Dr. Borghoff's research projects have been funded both by the Core research program and through specific research grants from Oxygenated Fuels Association, American Petroleum Institute, American Chemistry Council and ARCO (now Lyondell) Chemical Company. She has recently accepted an opportunity to consult for Huntsman Chemical Company which involves conducting a literature review on what is known on the health effects of methyl tertiary butyl ether.

**Edler, Lutz: German Cancer Research Center**

Dr. Edler is the Head of Biostatistics at the Research Programme Genome Research and Bioinformatics of the German Cancer Research Center in Heidelberg Germany. He holds a Dipl. Math (M.S.) Mathematics, Physics from the Albert-Ludwigs-University, Freiburg, FRG and a Dr. rer. nat (Ph.D.) Mathematics from Johannes-Gutenberg-University, Mainz, FRG. His major areas of research are: Mathematical-statistical modeling of carcinogenesis and risk assessment; Pharmacokinetics and development of methodology for clinical oncology with a strong emphasis on the application computational statistics; Statistical Computing; Biostatistical Methods in Design and Analysis of Experiments; Mathematical and Statistical Modeling in Oncology; and Survival Analysis and Clinical Trials.

From 1990-1991 he was a Visiting Scientist, National Institute of Environmental Health Sciences, Division of Biometry and Risk Assessment, Research Triangle Park, U.S.A.

He has listed the following "Expert Meetings" in which he has participated: (1994) DAAD, Bad Godesberg; (1994) Human PBPK Models for TCDD, NIEHS, Research Triangle Park, USA; (1994, 1998) EUROSTAT, Luxembourg; (1998) Risk Assessment of Electromagnetic Waves, US NIEHS, Tucson, AZ, USA; (2000) Risk Assessment of Dioxin, US EPA, Fort Collins, USA; 5th Framework Program, EU, Brussels; (1998) Rapporteur at EMF Science Review Symposium of the NIEHS, Phoenix, AZ; and (2002) Working Group of US-Vietnam Scientific Conference on Human Health and Environmental Effects of Agent Orange/Dioxins, March 2002, Hanoi, Rep Vietnam.

He is a member of the following professional societies: American Statistical Association (ASA); Drug Information Association (DIA); International Biometric Society, German Region (IBS.DR); International Society for Clinical Biostatistics (ISCB); International Association for Statistical Computing (IASC); Bernoulli Society; Deutsche Krebsgesellschaft (DKG); Gesellschaft fuer Medizinische Dokumentation und Statistik (gmds); and International Statistical Institute (ISI, elected).

Professional Activities include: (1991-1995) Scientific Secretary International Association for Statistical Computing (IASC); (1995-1997) Vice President of the International Association for Statistical Computing (IASC); (1999 -2001) President of the International Association for Statistical Computing (IASC); (1993-1997) Member of the Council of the German Region International Biometric Society; (1998-2002) Member of the Council of the International Biometric Society; and (1993- now) Member of the Animal Protection Commission at the RegPr. Karlsruhe. Currently he is 2002 Co-Organizer of the Session `Clinical Trial" at the International Biometric Conference, Freiburg, Germany; 2002 Coorganizer of the Session



AR100240

`Pharmacogenetics and Pharmacogenomics Data Analysis Methods in Future Clinical Trials', 38th DIA Annual Meeting, Chicago; 2003 Chair of the International Organizing Committee of the International Conference on Carcinogenesis Risk Assessment (ICCRA), Athens, Greece; and 2004 Co-Chair of the Local Organizing Committee of the Biometrical Colloquium of the German Region of the International Biometric Society, Heidelberg, Germany.

His grants include: (Feb. 1991) Visitor at the Universidad Nacional de Colombia at Bogota, Columbia; (1990) DFG Travel Grant for 48th Session of the ISI in Cairo, Egypt; (June, 1993) DAAD Travel Grant for a visiting lectureship in Columbia; (1995) DFG Travel Grant for 50th Session of the ISI in Beijing, China; (Sep-Dec 1995) Consulting National Institute of Statistical Sciences (NISS), Res.Triangle Park; and (Aug-Sep 2001) KOSEF-DFG Visiting Scientist Grant, Yonsei University, Seoul, South-Korea.

He serves on the following committees and Advisory Boards: Advisor for the Collaborative Project on Knowledgebased Systems in Medicine; Reviewer for the Government Department of Research and Technology Funding Programme; Reviewer for the DFG; - Extramural Review Board of the AIO (German Cancer Society); Project Assessment Committee of the Phase I/II Study Group of the AIO; Independent Safety Committee for Boehringer Mannheim Co.; and Reviewer for the German Cancer Society and Krebshilfe.

Currently his editorial tasks include: (since 1993) Associate Editor of Computational Statistics and Data Analysis (CSDA) and Associate Editor of ONKOLOGIE; (since 1994) Associate Editor of the Biometrical Journal (Biometrische Zeitschrift); (since 1999) Associate Editor of Journal of Cancer Research and Clinical Oncology; and (since 2002) Editor of the Virtual Online Journal "Biostatistics" (Elsevier, Publ.)

**Hattis, Dale: Clark University (Current member, SAB Environmental Health Committee)**

Dale Hattis is Research Professor with the Center for Technology Environment and Development (CENTED) of the George Perkins Marsh Institute at Clark University. For the past twenty-seven years he has been engaged in the development and application of methodology to assess the health ecological and economic impacts of regulatory actions. His work has focused on the development of methodology to incorporate interindividual variability data and quantitative mechanistic information into risk assessments for both cancer and non-cancer endpoints.

Specific studies have included quantitative risk assessments for hearing disability in relation to noise exposure renal effects of cadmium reproductive effects of ethoxyethanol neurological effects of methyl mercury and acrylamide and chronic lung function impairment from coal dust four pharmacokinetic-based risk assessments for carcinogens (for perchloroethylene ethylene oxide butadiene and diesel particulates) an analysis of uncertainties in pharmacokinetic modeling for perchloroethylene and an analysis of differences among species in processes related to carcinogenesis.

He has recently been appointed as a member of the Environmental Health Committee of the EPA Science Advisory Board and for several years he has served as a member of the Food Quality Protection Act Science Review Board. Currently he is also serving as a member of the National Research Council Committee on Estimating the Health-Risk-Reduction Benefits of Proposed Air Pollution Regulations.

The primary source of his recent cooperative agreement support is the U.S. Environmental Protection Agency and specifically the Office of Research and Development's National Center for Environmental Assessment. This research includes: (1) Age related differences in susceptibility to carcinogenesis; towards a quantitative analysis of empirical data. Instrument number (Term: April 2002-Sept 2003); (2) Methods for evaluating human interindividual variability regarding susceptibility to particulates (Term Sept 98--September 2002); and (3) also funding from the State of Connecticut to work on Child/Adult differences in pharmacokinetic parameters, as a subcontractor as part of a cooperative agreement.



AR100241

He has been a councilor and is a Fellow of the Society for Risk Analysis and serves on the editorial board of its journal Risk Analysis. He holds a Ph.D. in Genetics from Stanford University and a B.A. in biochemistry from the University of California at Berkeley.

**Hoel, David: Medical University of South Carolina (Current member, SAB Environmental Health Committee)**

David G. Hoel, Ph.D., is a Distinguished University Professor at the Medical University of South Carolina. Dr. Hoel received his A.B. degree in Mathematics and Statistics from the University of California at Berkeley and his Ph.D. from the University of North Carolina at Chapel Hill and has more than 25 years of experience as a biostatistician, toxicologist and environmental health researcher.

Dr. Hoel's research specialties include: environmental causes of cancer, risk assessment models; statistical and mathematical applications in biology and medicine; epidemiology; and radiation health effects. Dr. Hoel is widely published, having authored or co-authored over 160 journal articles and co-editor of several books and journals. He serves on a variety of national association committees and panels, such as a member of the Institute of Medicine, Agent Orange Committees, EPA's Science Advisory Board.

He is a member of the National Academy of Sciences Institute of Medicine, is a National Associate of the National Academy of Sciences and National Research Council and a Fellow for the American Association for the Advancement of Science. Before joining the faculty at the Medical University Dr. Hoel was a division director at the NIEHS of NIH. This division was made up of four branches with responsibility for the Institute's program in biostatistics, epidemiology and molecular toxicological risk assessment.

Sources of recent grant and/or contract support: include: (1) Savannah River Site Former Production Workers Medical Surveillance Program – Phase II Year Continuation (funded by the Department of Energy)--the goal of this project is to assess occupational exposures reviewed by former DOE workers at SRS and conduct appropriate medical examinations in order to evaluate work related illness and risk.; (2) "Low Dose Radiation Project" (funded by the Department of Energy, Environmental Biosciences Program); the goal of this project is to develop methods for estimating cancer risks from low dose and low dose rate ionizing radiation; (3)."Radiation Leukemogenesis: Applying Basic Science to Epidemiology Estimates of Low Dose Risks and Dose-Rate Effects"(funded by the Department of Energy)--the goal of this project is to incorporate biological information into mathematical models of radiation induced leukemias; and (4)"Radiation Risk Analysis: Model Issues and Interspecies Extrapolation"(funded by the National Opinion Research Center/NASA)--the goal of this project is to use and evaluate experimental animal data for estimation of human health risks from radiation.

**Lambert, George: Robert Wood Johnson Medical School/ University of Medicine and Dentistry of New Jersey (Current member, SAB Environmental Health Committee)**

Dr. Lambert is Associate Professor of Pediatrics, Director Division of Pediatric Pharmacology and Toxicology at the University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School – Piscataway/New Brunswick. He is also the Director of the NIEHS/EPA Center for Childhood Neurotoxicology and Exposure Assessment, which is located at the Environmental and Occupational Health Sciences Institute, a jointly sponsored institute of Rutgers, The State University of New NJ and UMDNJ-Robert Wood Johnson Medical School

He holds a B.S. in zoology from University of Illinois, Champaign-Urbana (1968) and an M.D. from the University of Illinois, Chicago, IL (1972).

Recent grants and other outside funding sources include the following: (1) a grant to study the Reproductive Outcomes of the World Trade Center Tragedy (funded by National



AR100242

Institute of Environmental Health Sciences) (2) a grant to determine the influences of environmental exposure to neurotoxicants on child neurological health and development with special emphasis on autism and related disabilities (funded jointly by the National Institute of Environmental Health Sciences and the Environmental Protection Agency) (3) a grant to study the effects of Herbal Phytoestrogens & Prostate Cancer (funded by the Cancer Commission of New Jersey); (4) Effects of eating Crabs with PCBs and Dioxin Laden on Human Health (funded by the New Jersey Department of Environmental Regulations); (5) a grant to study the role of gene polymorphisms in Birth Defects. (funded jointly by the Centers for Disease Control and the NJ State Birth Defects Registry); and (6) the correlation between hypospadism and xenoestrogens (funded jointly by the Centers for Disease Control and the New Jersey Department of Health).

**Lemasters, Grace: University of Cincinnati (Current member, SAB Environmental Health Committee)**

Dr. Lemasters is a Professor in the Division of Epidemiology and Biostatistics Department of Environmental Health, College of Medicine, University of Cincinnati and former head of Epidemiology and Biostatistics in the Department of Environmental Health, College of Medicine.

She holds a Ph.D., Department of Environmental Health, College of Medicine, University of Cincinnati, Epidemiology and Environmental Health Science; M.S.N, University of Cincinnati; and a B.S.N., Indiana University.

For almost three decades she has conducted researched in occupational and environmental epidemiology and investigating health effects including ergonomics and musculoskeletal research, respiratory disease, cytogenetic effects, and childhood allergy and asthma. Dr. LeMasters is a national and international expert in occupational and environmental health studies and has published numerous scientific articles and book chapters book in the areas of exposures and health effects and study design methodologies.

She has conducted research on men and women in the military for over 15 years examining the effects of exposures to fuels and solvents on cytogenetics, female hormones, male reproduction and neurological effects. Other areas of research include a 15-year pulmonary longitudinal study of the health effects of refractory ceramic fiber exposure (substitute for asbestos) and lung cancer and lung disease. She has recently received funding as the principle investigator on a 5-year study on diesel exposure and atopy and respiratory disorders in children. Other current research includes the following: caffeine effects on female hormones during early pregnancy, occupational risk factors related to falls, and exposures of women in the military to jet fuel and hormonal changes.

Among her service on Committees and Associations she lists: Federal Advisory Committee on Children's Health NICHD (2002- ); Armed Forces Epidemiological Board (2001-present); Reviewer Department of Defense PRMRP (July 11-13, 2001; Member National Toxicology Program Board of Scientific Counselors of the Office of the Assistant Secretary and Surgeon General (1999-2002); Editorial Board: Occupational and Environmental Medicine (1996-2001); Editorial Board: Journal of Reproductive Toxicology (1991-); Fellow, American College of Epidemiology; Member, Society for Epidemiology Research; and Member: Sigma Theta Tau Alpha and Beta Honors Chapters.

Current sources of recent grant and/or contract support are the: Environmental Protection Agency; NIH-CDC/NIOSH; NIH-NIEHS; and the Refractory Ceramic Fiber Coalition.



AR100243

**Li, Abby: Monsanto Company (Current member, SAB Environmental Health Committee)**

Dr. Abby Li received her Ph.D. from the University of Chicago in pharmacology and physiology. She is currently a Senior Science Fellow at Monsanto. She is a toxicologist in the Department of Toxicology and Human Health Risk Assessment. She has specialized expertise in neurotoxicology as well as product stewardship responsibilities involving general toxicology, exposure and risk assessment issues. Dr. Li has conducted numerous studies primarily for regulatory submission in neurotoxicology in adult and developing rats, in humans and in vitro systems.

She was Monsanto's Neurotoxicology Team Leader responsible for developing testing capabilities at Monsanto including motor activity, schedule controlled operant behavior, functional observational battery, auditory startle habituation, learning and memory and neuropathology. She has also conducted in vivo pharmacokinetic studies (ADME studies) and in vitro metabolism studies. Dr. Li served on the Editorial Board of Neurotoxicology from 1995-2001.Dr. Li was invited by the US EPA country representative to serve on the US team of experts to develop international OECD guidelines on neurotoxicity (1995 - 1998) and developmental neurotoxicity (1996-2000). Dr. Li is the Chair of the Neurotoxicology Technical Panel of the American Chemistry Council's Long Range Initiative (ACC LRI) responsible for funding research to advance the field of neurotoxicology in focus areas such as susceptible populations, and in developing new methods for hazard and exposure assessment. She served as Co-Chair of Crop Life America's Developmental Neurotoxicology Working Group in 2000 and is currently a member of this group. She is a member of the EPA's Science Advisory Board's Environmental Health Committee and reviewed the EPA's 1999 draft cancer guidelines, the RfC Methods Case Studies, and the Lead 403 Rule among other draft assessments. Dr. Abby Li was a peer consultant to the September 10-11, 1996 EPA Benchmark Dose Peer Consultation Workshop

**Luderer, Ulrike: University of California at Irvine (Current member, SAB Environmental Health Committee)**

Dr. Ulrike Luderer is Assistant Professor of Medicine in the Division of Occupational and Environmental Medicine at the University of California at Irvine. She also holds joint appointments in the Departments of Developmental and Cell Biology and Environmental Toxicology. Dr. Luderer's research focuses on mechanisms of action of reproductive toxicants and on protective mechanisms against those toxicants. She is a recipient of a National Institute of Environmental Health Sciences research grant (2002-2007) entitled "Glutathione:Protecting Ovarian Follicles from Oxidant Injury" and a co-investigator on an EPA grant "Latent Effects of Gestational Exposure to Heptachlor" She has published peer-reviewed journal articles and book chapters and presented research at national and international scientific conferences on such topics as the effects of toluene exposure on reproductive endocrine function, the functions of and regulation of glutathione in the ovary, the differential regulation of follicle-stimulating hormone and luteinizing hormone secretion, and reviews of reproductive and developmental and endocrine toxicology. She has served on the National Toxicology Program/NIEHS Center for the Evaluation of Risks to Human Reproduction Expert Panel on 1- and 2-Bromopropane and on the National Research Council subcommittee on methyl bromide. She is currently a member of the EPA SAB's Environmental Health Committee. Dr. Luderer has a Ph.D. in reproductive endocrinology and an M.D. from Northwestern University and is board-certified in Internal Medicine and in Occupational and Environmental Medicine. She has a Sc.B. in biomedical engineering from Brown University.



AR100244

**McClain, Michael: McClain Associates**

Dr. R. Michael McClain is currently an Adjunct Professor University of Medicine and Dentistry of NJ and now works primarily as a consultant in toxicology. He was formerly a Distinguished Research Leader and Director of Toxicology, Hoffmann-La Roche, Inc. Dr. McClain received his Ph.D. from the Department of Pharmacology at the University of Iowa and B.S. and M.S. degrees from Duquesne University. Dr. McClain is a Diplomate of the American Board of Toxicology and a Fellow of the Academy of Toxicological Sciences. He has worked in the pharmaceutical industry for over 30 years in the areas of teratology and reproductive toxicology, general toxicology and carcinogenicity testing. His research activities are involved primarily in mechanisms of chemical carcinogenesis for thyroid, liver and adrenal and regulatory aspects for cancer risk assessment. He has been active in the Pharmaceutical Research and Manufactures Association and PhRMAs efforts on harmonizing international guidelines for drug development (ICH). He has been involved with the ILSI organization and served as President of the ILSI's Health and Environmental Science Institute (HESI) and as a member of ILSI's Board of Trustees. Dr McClain is a member of the National Advisory Environmental Health Sciences Council for NIEHS. Dr. McClain is also active in the Society of Toxicology having served a term as Treasurer and as President of the Society in 1998

**Melnick, Ronald: National Institute of Environmental Health Sciences**

Dr. Melnick is a Senior Toxicologist and Director of Special Programs in the Environmental Toxicology Program at the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health in Research Triangle Park, North Carolina. Prior to this position he was Group Leader of the Toxicokinetic and Biochemical Modeling Group in the Laboratory of Computational Biology and Risk Analysis at NIEHS. Dr. Melnick obtained his B.S. degree from Rutgers University and his Ph.D. in food science/biochemistry from the University of Massachusetts at Amherst. He was a postdoctoral research fellow in the Department of Physiology-Anatomy at the University of California in Berkeley and then an assistant professor of life sciences at the Polytechnic Institute of New York. At NIEHS he has been involved in the design, monitoring and interpretation of NTP toxicity and carcinogenesis studies, as well as mechanistic studies to characterize the behavior of environmental carcinogens. He spent one year as an agency representative to the White House Office of Science and Technology Policy to work on interagency assessments of health risks of environmental agents and on risk assessment research needs in the Federal government. Dr. Melnick has organized several national and international symposiums and workshops on health risks associated with exposure to environmental and occupational toxicants. He has also served on numerous scientific review and advisory panels, including the working group of the International Agency for Research on Cancer (1995) that classified trichloroethylene as probably carcinogenic to humans. Dr. Melnick has served on several committees at NIEHS, including Chair of the Toxicokinetic Faculty and member of the NIEHS review group for the NTP Report on Carcinogens. The latter group reviewed data on trichloroethylene for listing in the Report on Carcinogens. Dr. Melnick is a Fellow of the Collegium Ramazzini. As a federal employee, he does not receive any grant or contract support.

**Solomon, Gina: Natural Resources Defense Council**

Dr. Gina Solomon is a Senior Scientist at the Natural Resources Defense Council in San Francisco and an Assistant Clinical Professor of Medicine at the University of California at San Francisco. Dr. Solomon is a specialist in internal medicine, preventive medicine, and occupational and environmental medicine. Her work has focused on environmental and occupational threats to reproductive health and child development. She attended medical school

at Yale and underwent post-graduate training in medicine and public health at Harvard. Dr. Solomon served on the U.S. EPA's Federal Advisory Committee on endocrine disrupting chemicals and is a scientific advisor to numerous organizations including the California Department of Health Services Environmental Epidemiology Section and the Pediatric Environmental Health Specialty Unit at U.C. San Francisco. Dr. Solomon has published peer-reviewed articles on various topics, including solvents and miscarriage, endocrine disruptors, diesel exhaust and asthma, and contaminants in breast milk. She is a co-author of the book, Generations at Risk: Reproductive Health and the Environment, published by MIT Press in 1999.

**Whyatt, Robin: Department of Environmental Health Sciences**

Dr. Robin Whyatt is Deputy Director of the Columbia Center for Children's Environmental Health and is Assistant Professor in the Department of Environmental Health Sciences at the Mailman School of Public Health, Columbia University. Dr. Whyatt's research focus is on the effects of environmental exposures on women and children, including the developing fetus. Prior to coming to Columbia in 1991, she evaluated the extent of pesticide exposure in the preschooler's diet as Senior Staff Scientist at the Natural Resources Defense Council (NRDC). Her research at Columbia University has used biologic markers to study effects of environmental exposures during pregnancy. This has included a molecular epidemiologic study of prenatal exposures to ambient air pollution and cigarette smoking in Poland. Dr. Whyatt's is currently collaborating on a comprehensive community-based study of environmental risks to African American and Dominican mothers and newborns in Northern Manhattan and the South Bronx. The prospective cohort study is evaluating effects of environmental exposures on fetal growth, neurocognitive developmental and asthma risk. Dr. Whyatt's focus is on the extent of exposure to non-persistent pesticides (organophosphates, carbamates and pyrethroids) during pregnancy among this minority population. Dr. Whyatt is also collaborating with the Center for Disease Control on the validation of biomarkers of exposure to contemporary-use pesticides during pregnancy. Dr. Whyatt has published widely on the application of biologic markers to studies of environmental risks to infants and children and on the effects of environmental exposures during fetal development. She is currently principal investigator on three grants: a U.S. EPA STAR grant to validate the measurement of non-persistent pesticides in postpartum meconium as a biomarker of fetal exposure; a NIEHS RO1 grant to validate a battery of biomarkers of prenatal exposure; and on an intervention grant from the Speaker's Fund for Public Health Research to reduce residential pesticide exposures during pregnancy. Dr. Whyatt served on the U.S. EPA Workshop, Critical Windows of Exposure for Children's Health, and on the U.S. EPA Workshop, Technical Workshop on Issues Associated with Considering Developmental Changes in Behavior and Anatomy when Assessing Exposure to Children. She was Co-chair of the Symposium on Alternative Human Matrices for Biomonitoring, at the 2001 International Agency for Exposure Assessment, Charleston, South Carolina and is currently serving on the Exposures to Chemical Agents Work Group of the National Children's Longitudinal Cohort Study. Dr. Whyatt received her Doctorate in Public Health (Dr.P.H.) from Columbia University with honors in 1995 and her Masters in Public Health (M.P.H) from Columbia University in 1985.

**Yang,Raymond: Colorado State University**

Raymond S. H. Yang is presently Professor of Toxicology and Director of Center for Environmental Toxicology and Technology, one of 14 Programs of Research and Scholarly Excellence at Colorado State University (CSU). Between July 1990 and June 1995, Dr. Yang served as the Head, Department of Environmental Health, College of Veterinary Medicine and Biomedical Sciences, CSU, Fort Collins, CO. Prior to joining CSU in 1990, Dr. Yang spent



AR100246

seven years each in chemical industry (Bushy Run Research Institute, Union Carbide - Mellon Institute, 1976 - 1983) and in the federal government [National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP), 1983 - 1990].

Dr. Yang received his B.S. in Biology from the National Taiwan University in 1963; M.S. and Ph.D. in Toxicology/Entomology from North Carolina State University in 1967 and 1970, respectively. Between 1970 and 1973, he was a postdoctoral fellow at Cornell University. Between 1973 and 1976, he was Research Associate and then Assistant Professor at the Institute of Comparative and Human Toxicology, Albany Medical College. Dr. Yang had also been appointed Adjunct Associate Professor at University of Pittsburgh and Adjunct Professor at North Carolina State University.

Dr. Yang's research expertise and interests cover many subdisciplines in toxicology, including toxicology of chemical mixtures, toxicologic interactions, physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling, biologically based dose-response (BBDR) modeling, carcinogenesis and neuro-developmental toxicology. Between 1992 and 2000, he served as the Program Director of the NIEHS Superfund Basic Research Program Project at CSU and since the summer of 1999 he has been the Program Director for an NIEHS Quantitative Toxicology Training Grant. Since 1990, Dr. Yang has been developing an interdisciplinary research program on Quantitative and Computational Toxicology using the central theme of PBPK/PD, BBDR, and reaction network modeling of chemicals and chemical mixtures at CSU.

Dr. Yang's committee work includes serving as a Committee or Expert Panel Member for the following Committee/Panel or organizations: National Academy of Sciences/National Research Council Safe Drinking Water Subcommittee on Mixtures; USEPA/Environmental Criteria Assessment Office (ECAO); Screening and Testing Work Group of the Endocrine Disruptor Screening and Testing Advisory Committee, USEPA; Electric Power Research Institute (EPRI); Expert Panel Member, Risk Assessment for Mixtures of Drinking Water Disinfection-Byproducts, International Life Sciences Institute/USEPA; Institute of Medicine, National Academy of Sciences Committee to Study the Interactions of Drugs, Biologics, and Chemicals in Deployed U. S. Military Forces; Chair for a Chemical Mixture Workshop Agency for Toxic Substances and Disease Registry (ATSDR); Health Council of the Netherlands; Society of Toxicology Expert Panel on Chemical mixtures; Chemical Mixture Committee member to National Occupational Research Agenda, NIOSH; and NIEHS Environmental Health Sciences Review Committee. Dr. Yang's research support came principally from the National Institute of Health (NIH), U.S. Air Force, U.S. Environmental Protection Agency (EPA), ATSDR, and Center for Disease Control and Prevention (CDC)/National Institute of Occupational Safety and Health (NIOSH).



AR100247