



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

July 15, 2002

OFFICE OF
THE ADMINISTRATOR
EPA SCIENCE ADVISORY BOARD

Note to the Reader:

The attached draft report is a draft report of the EPA Science Advisory Board (SAB). The draft is still undergoing final internal SAB review, however, in its present form, it represents the consensus position of the panel involved in the review. Once approved as final, the report will be transmitted to the EPA Administrator and will become available to the interested public as a final report.

This draft has been released for general information to members of the interested public and to EPA staff. This is consistent with the SAB policy of releasing draft materials only when the Committee involved is comfortable that the document is sufficiently complete to provide useful information to the reader. The reader should remember that this is an unapproved working draft and that the document should not be used to represent official EPA or SAB views or advice. Draft documents at this stage of the process often undergo significant revisions before the final version is approved and published.

The SAB is not soliciting comments on the advice contained herein. However, as a courtesy to the EPA Program Office that is the subject of the SAB review, we have asked them to respond to the issues listed below. Consistent with SAB policy on this matter, the SAB is not obligated to address any responses that it receives. Responses are due no later than July 17, 2002

1. Has the Committee adequately responded to the questions posed in the Charge?
2. Are any statements or responses made in the draft unclear?
3. Are there any technical errors?

For further information or to respond to the questions above, please contact:

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7

1 INSERT DATE

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3 EPA-SAB-EHC-XXX-02-XXX

4
5 The Honorable Christine Todd Whitman
6 Administrator
7 U.S. Environmental Protection Agency
8 1200 Pennsylvania Avenue, N.W.
9 Washington, D.C. 20460

10
11 Subject: Review of Draft Trichloroethylene Health Risk
12 Assessment: Synthesis and Characterization

13
14 Dear Governor Whitman:

15
16 A Panel of the U.S. EPA Science Advisory Board's Environmental Health
17 Committee met on June 18-19, 2002 to review the Agency's draft assessment,
18 "Trichloroethylene Health Risk Assessment: Synthesis and Characterization."

19
20 The Board advises the Agency to move ahead to revise and complete this
21 important draft assessment. It addresses a chemical, trichloroethylene (TCE), significant
22 for being a nearly ubiquitous environmental contaminant in both air and water, being a
23 common contaminant at Superfund sites, and because it is "listed" in many Federal
24 statutes and regulations. The draft assessment is also important because it sets new
25 precedents for risk assessment at EPA. We believe the draft assessment is a good starting
26 point for completing the risk assessment of TCE. The Panel commends the Agency for
27 its effort and advises it to proceed to revise and finalize the draft assessment.

28
29 The Board commends the Agency for its groundbreaking work in this draft
30 assessment in several important new areas in risk assessment: a) risk to children and other
31 susceptible populations; b) cumulative risk; c) examination of multiple kinds of evidence
32 including evidence about physiological and molecular modes of action; d) the assessment
33 of the health risks associated with the many metabolites of TCE; e) the use of
34 biologically-based modeling; f) the explicit recognition and acknowledgement of
35 uncertainties in the risk analysis; g) the consideration of multiple data sets from animal
36 and human studies to derive cancer slope factors.

37
38 Although the Board welcomes this effort, it also cautions the Agency that the new
39 areas explored involve considerable uncertainty. Progress in reducing these uncertainties
40 will be an evolutionary process that will necessitate advancements in scientific research
41 and analysis. The Board also notes that there is a need for Agency wide guidance in many
42 of the areas explored in the draft assessment. The Agency should develop consistent
43 policies across program areas on protection of children and other vulnerable populations,
44 cumulative risk, and aggregate risk.

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Dr. William Glaze, Chair
EPA Science Advisory Board

Dr. Henry Anderson, Chair
Trichloroethylene Health Risk
Assessment: Synthesis and
Characterization Review Panel

NOTICE

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4 This report has been written as part of the activities of the EPA Science Advisory
5 Board, a public advisory group providing extramural scientific information and advice to
6 the Administrator and other officials of the Environmental Protection Agency. The
7 Board is structured to provide balanced, expert assessment of scientific matters related to
8 problems facing the Agency. This report has not been reviewed for approval by the
9 Agency and, hence, the contents of this report do not necessarily represent the views and
10 policies of the Environmental Protection Agency, nor of other agencies in the Executive
11 Branch of the Federal government, nor does mention of trade names or commercial
12 products constitute a recommendation for use.

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30 EPA Administrator, senior Agency management, appropriate program staff, interested
31 members of the public, and is posted on the SAB website (www.epa.gov/sab).
32 Information on its availability is also provided in the SAB's monthly newsletter
33 (Happenings at the Science Advisory Board). Additional copies and further information
34 are available from the SAB Staff [US EPA Science Advisory Board (1400A), 1200
35 Pennsylvania Avenue, NW, Washington, DC 20460-0001; 202-564-4533].

1 **ABSTRACT**

1 **U.S. Environmental Protection Agency**
2 **Science Advisory Board**
3 **Environmental Health Committee**
4 **Trichloroethylene Health Risk Assessment:**
5 **Synthesis and Characterization Review Panel***
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7
8

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1	TABLE OF CONTENTS
2	
3	1. EXECUTIVE SUMMARY OF RESPONSES TO CHARGE QUESTIONS
4	
5	2. INTRODUCTION
6	2.1. Background
7	2.2. Process for Developing this Report
8	
9	3. CHARGE QUESTION 1
10	3.1. Agency Charge Question and Suggested Areas for Inquiry
11	3.2. Panel Response
12	
13	4. CHARGE QUESTION 2
14	4.1. Agency Charge Question and Suggested Areas for Inquiry
15	4.2. Panel Response
16	4.2.1. Human Epidemiological Studies
17	4.2.2. Animal Toxicology
18	
19	5. CHARGE QUESTION 3
20	5.1. Agency Charge Question and Suggested Areas for Inquiry
21	5.2. Panel Response
22	
23	6. CHARGE QUESTION 4
24	6.1. Agency Charge Question and Suggested Areas for Inquiry
25	6.2. Panel Response
26	
27	7. CHARGE QUESTION 5
28	7.1. Agency Charge Question and Suggested Areas for Inquiry
29	7.2. Panel Response
30	7.2.1. The Range of Risk Estimates
31	7.2.1.1 Clarification of the Cancer Slope Factors
32	7.2.1.2 Suitability and Use of the Cancer Slope Factors
33	7.2.1.3 Improved Mediation of the Cancer Slope Factors
34	7.2.2. Further Studies to Be Included
35	7.2.3. Linear or Nonlinear Approach
36	7.2.4. For Further Consideration
37	
38	8. CHARGE QUESTION 6
39	8.1. Agency Charge Question and Suggested Areas for Inquiry
40	8.2. Panel Response
41	8.2.1. Modeling
42	8.2.2. Uncertainty Analysis
43	8.2.3. Data Availability
44	8.2.4. Markov-Chain Monte Carlo (MCMC)
45	8.2.5. For Further Consideration
46	

1 9. CHARGE QUESTION 7

2 9.1. Agency Charge Question and Suggested Areas for Inquiry

3 9.2. Panel Response

4

5 10. CHARGE QUESTION 8

6 10.1. Agency Charge Question and Suggested Areas for Inquiry

7 10.2. Panel Response

8

9 11. CHARGE QUESTION 9

10 11.1. Agency Charge Question and Suggested Areas for Inquiry

11 11.2. Panel Response

12 11.2.1. Major Summary Consensus Points of the Panel

13 11.2.2. Background to the Panel's Conclusions

14 10.2.3. How the Draft Assessment Can be Improved

15

16 REFERENCES

17

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

21

22 APPENDIX B: SPECIFIC PANEL COMMENTS ON THE AGENCY'S ASSESSMENT
23 OF NONCANCER ENDPOINTS

24 1. Specific Comments on Hazard Characterization for Noncancer Endpoints

25 1.1. Liver Effects

26 1.2. Kidney Effects

27 1.3. Developmental Effects

28 1.4. Neurotoxicity Effects

29 1.5. Endocrine System Effects and Reproductive Toxicity Effects

30 2. Specific Comments on Uncertainty Factors for NonCancer Endpoints

31 2.1. Human Variation

32 2.2. Animal-to-Human Uncertainty

33 2.3. Subchronic-to-Chronic Uncertainty

34 2.4. LOAEL to NOAEL Uncertainty

35 2.5. Other Factors

36

1 1. EXECUTIVE SUMMARY OF RESPONSES TO CHARGE QUESTIONS

2
3 a) Charge Question 1: Does the assessment adequately discuss the likelihood that
4 trichloroethylene (TCE) acts through multiple metabolites and multiple modes of action?

5
6 Panel's Response: EPA should be commended for its efforts to date to evaluate a
7 wide variety of hypotheses for the carcinogenic and other toxic effects of TCE. The draft
8 assessment could be enhanced by considering additional selective quantitative analysis
9 and further evaluation of dose-response relationships, especially of the relative likelihood
10 of the different metabolites to play a role in the toxicity of TCE at human exposure
11 levels. Panel members offered several examples of quantitative analyses that the Agency
12 could use to improve the document.

13
14 b) Charge Question 2: Is the cancer weight-of-evidence characterization
15 adequately supported?

16
17 Panel's Response: The Panel agreed that the cancer weight-of-evidence
18 characterization is adequately supported. Members of the Panel commended EPA for
19 compiling such an extensive array of scientific literature including over 80
20 epidemiological studies and hundreds of toxicological and mechanistic studies, and
21 summarizing the evidence relatively clearly and cohesively. The panel endorsed EPA's
22 use of a combination of human epidemiological studies, animal toxicology studies, and
23 mechanistic data to make a cancer risk determination.

24
25 c) Charge Question 3: A new feature of the cancer database is molecular
26 information on the von Hippel-Lindau tumor suppressor gene. Is this information
27 adequately discussed and are the conclusions appropriate?

28
29 The consensus of the panel is that the discussion in the draft assessment is
30 generally appropriate. There was a recommendation to strengthen the description from
31 the "suggestive evidence" referred to on line 8 of page 3-38. The panel generally agreed
32 that EPA is wise not to regard the evidence as entirely conclusive pending independent
33 confirmation by another group. The discussion in the draft assessment might be
34 improved by including some additional comparative observations from kidney cancers
35 not in the TCE exposed workers. Panel members offered the following enhanced
36 discussion as a starting point for EPA consideration.

37
38 d) Charge Question 4: Does the assessment adequately discuss the use of multiple
39 critical effects in developing an oral reference dose (RfD) and inhalation reference
40 concentration (RfC) for effects other than cancer? Are the uncertainty factors well
41 discussed and well supported?

42
43 The Panel commended the Agency for consideration of multiple noncancer
44 endpoints. It noted that TCE clearly has important hepatotoxic, nephrotoxic, neurotoxic,
45 immunologic, developmental and reproductive effects that should be considered in the
46 derivation of the RfD and RfC. The Panel advised the Agency to strengthen the

1 characterization of the data at each site of toxicity and to discuss and characterize more
2 clearly and comprehensively the evidence supporting alternative positions for derivation
3 of the RfD and RfC. A special focus for discussion was the derivation of uncertainty
4 factors for the RfD and RfC. The Panel advised the Agency to explain more clearly in
5 the draft assessment how uncertainty factors were derived for the RfD and RfC and it
6 outlined a spectrum of views about how to interpret the science underlying these factors.

7
8 e) Charge Question 5: Does the assessment adequately discuss the derivation of a
9 range of estimates for the cancer risk? Are there any studies that should/should not have
10 been included?

11
12 The Panel commended EPA for the derivation of a set of cancer risk estimates or
13 cancer slope factors (CSF) for TCE in the draft assessment. The presentation of a range
14 of estimates is a step forward for EPA towards a more explicit and more quantitative
15 representation of the substantial uncertainties in estimates of cancer risks.

16
17 The Panel identified a key study (Hansen et. al., 2001) to be included in the
18 revision of the draft assessment and also emphasized that where epidemiological studies
19 are the basis of risk estimates, EPA needs to consider the full array of studies for each
20 cancer site where exposure estimates are possible. The Panel commended the Agency for
21 providing sections on sensitive populations and cumulative risks and added several
22 suggestions for strengthening quantitative aspects of the risk assessment methodology
23 that are important for the refinement of the risk assessment of TCE.

24
25 f) Charge Question 6: Please comment on the use of calibrated models and
26 uncertainty analysis to address the question of pharmacokinetic model uncertainty.

27
28 The Panel commended the Agency's recognition of model uncertainty in the draft
29 assessment. It advises the Agency to explain the modeling methods, and to make the
30 models, data, and assumptions used available, so that the Agency's results can be
31 reproduced. The Panel called on the Agency to compare the two calibrated models used
32 and to show how the models and analyses compare and relate to one another. The Panel
33 advises the Agency to highlight the impact of the uncertainty analysis on the dose
34 estimated of the different models and on the dose-response analysis and to explain the
35 differences between the models and the ranges of uncertainty.

36
37 g) Charge Question 7: Is it appropriate to consider background exposures and
38 other characteristics of an exposed population as modulating the risk of TCE exposure in
39 that population?

40
41 The Panel was pleased that the Agency has taken the first steps of including the
42 issue of cumulative risk in a health risk assessment. Although there was agreement that
43 background exposures to TCE and/or metabolites is a very important issue, there was
44 disagreement about whether the RfD, and the uncertainty factor used to derive it, should
45 be the method by which this background exposure is addressed. The Panel agreed,
46 however, that regardless of EPA's final policy decision on whether or not to include an

1 additional uncertainty factor in the RfD for background exposure, more attention and
2 detail is needed to provide a rationale for the Agency's use of such an uncertainty factor.

3
4 h) Charge Question 8: Do the data support identifying risk factors that may be
5 associated with increased risks from TCE exposure? Are there any risk factors that
6 should/should not have been included?

7
8 The Panel found that the data support identifying numerous risk factors that may
9 be associated with increased risks to susceptible subpopulations from TCE exposure.
10 The EPA draft assessment has done a good job identifying the general areas of concern
11 related to prenatal, reproductive and developmental risks associated with TCE exposure,
12 especially given the level of information known to date. The Panel agreed with the draft
13 risk assessment's identification of multiple background exposures to ethanol, TCE, and
14 its metabolites, and other chemical solvent mixtures as factors that may be associated
15 with increased risks.

16
17 i) Charge Question 9: Do the data support the possibility that TCE can affect
18 children and adults differently? Should this be reflected in the quantitative assessment?

19
20 Panel Response: The Panel reached consensus on the following conclusions related to
21 this charge question: a) the data presented supports the possibility that TCE can affect
22 children differently than adults, although there is a very limited database of TCE in
23 children due to lack of directly applicable studies; b) the draft does not explicitly discuss
24 whether or not the uncertainty factors address risk to children or attempt to develop
25 toxicity values that take children into consideration; c) the Panel advises the Agency to
26 develop a stand-alone comprehensive children's chapter that discusses all the children's
27 issues, including exposure, susceptibility during pregnancy, pharmacokinetics, and
28 pharmacodynamics, in addition to discussions of developmental animal and children data
29 in every section; and d) the Panel advises the Agency to support statements about
30 differences between children and adults with a quantitative discussion, whenever
31 possible. Although the Panel differed on the question of whether the Agency should add
32 a quantitative uncertainty factor to protect children above the composite uncertainty
33 factor already in the draft assessment, it did advise the Agency to explicitly this issue and
34 to clarify how such a factor would relate to other uncertainty factors used.

1 2. INTRODUCTION

2
3 2.1. Background

4
5 The purpose of this report is to provide advice to the Agency in developing a final
6 health risk assessment for TCE. The SAB formed the Trichloroethylene Health Risk
7 Assessment: Synthesis and Characterization Review Panel to review a draft assessment
8 dated August 2001 that EPA's Office of Research and Development (ORD) provided for
9 external public comment on September 19, 2001. TCE is a major contaminant of concern
10 in EPA's air, water, and waste programs. EPA's regulatory program and regional offices
11 have identified TCE as among the highest priorities for a new assessment.

12
13 The Agency has noted, and the Panel acknowledges, that the draft assessment
14 submitted for review was shaped by several new developments in risk assessment. The
15 practice of risk assessment has been evolving from a focus on a single toxic effect of one
16 pollutant in one environmental medium toward integrated assessments covering multiple
17 effects and multiple media and incorporating information about mode of action,
18 uncertainty, human variation, and cumulative effects of multiple pollutants in different
19 media. This evolution has responded to recommendations of the National Research
20 Council, whose recommendations have been embraced in EPA's proposed cancer
21 guidelines.

22
23 The TCE draft assessment breaks new ground in addressing the new dimensions
24 of risk assessment that EPA and others have advocated. The draft assessment discusses
25 the possibility that children, infants, and the developing fetus may differ from adults with
26 respect to susceptibility to TCE's toxic effects. The assessment also addresses cumulative
27 risks by discussing the implications of other chlorinated solvents and agents that have
28 metabolic pathways, potential modes of action, and toxic effects similar to TCE. The
29 assessment implements principles of the proposed cancer guidelines by emphasizing
30 characterization discussions, and by using information on mode-of-action, information on
31 susceptible populations to derive cancer slope factors and RfD and RfC values

32
33 The issues surrounding TCE are quite complex, with extensive information in
34 some areas and relatively little information in others. EPA's ORD initiated development
35 of 16 peer-reviewed state-of-the-science papers that were published in a special
36 supplementary issue of the journal Environmental Health Perspectives (May 2000). The
37 Agency acknowledged that it relied on those papers as the primary scientific support for
38 the draft assessment.

39
40 In the fall of 2001, EPA asked the SAB to convene a Panel to address the
41 following draft Charge:

- 42
43 a) Does the assessment adequately discuss the likelihood that
44 trichloroethylene (TCE) acts through multiple metabolites and multiple modes of action?
45
46 b) Is the cancer weight-of-evidence characterization adequately supported?

1
2 c) A new feature of the cancer database is molecular information on the von
3 Hippel-Lindau tumor suppressor gene. Is this information adequately discussed and are
4 the conclusions appropriate?

5
6 d) Does the assessment adequately discuss the use of multiple critical effects
7 in developing an oral reference dose (RfD) and inhalation reference concentration (RfC)
8 for effects other than cancer? Are the uncertainty factors well discussed and well
9 supported?

10
11 e) Does the assessment adequately discuss the derivation of a range of
12 estimates for the cancer risk? Are there any studies that should/should not have been
13 included?

14
15 f) Please comment on the use of calibrated models and uncertainty analysis
16 to address the question of pharmacokinetic model uncertainty.

17
18 g) Is it appropriate to consider background exposures and other
19 characteristics of an exposed population as modulating the risk of TCE exposure in that
20 population?

21
22 h) Do the data support identifying risk factors that may be associated with
23 increased risks from TCE exposure? Are there any risk factors that should/should not
24 have been included?

25
26 i) Do the data support the possibility that TCE can affect children and adults
27 differently? Should this be reflected in the quantitative assessment?

28 29 2.2. Process for Developing this Report

30
31 The SAB formed a special panel to address the Agency's charge questions. It was
32 composed of members of the SAB's Environmental Health Committee, augmented to
33 provide additional expertise needed to address the charge and to provide breadth of
34 viewpoints on issues key to the review. Panel members were added to provide expertise
35 in the following areas: TCE epidemiology; pharmacokinetic modeling; cancer toxicity
36 biostatistics, and modeling; modes of action at the molecular level; modes of action at the
37 physiological level; differing perspectives on how the toxicology database of information
38 on TCE can be understood; and risk assessment expertise. Biosketches of panel members
39 can be found in Appendix A.

40
41 The Panel reviewed the Agency's draft assessment, along with supplementary
42 background information that included: a) Environmental Health Perspectives (May
43 2000); b) Summary of Public Comments for EPA's Science Advisory Board; c) Log of
44 public comments for "Trichloroethylene (TCE) Health Risk Assessment Synthesis and
45 Characterization;" and d) over 800 pages of public comments.

46

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

5
6 The Panel held a face-to-face public meeting in Washington D.C. on June 18-19,
7 2002, and a public teleconference to discuss this report in draft form on July 18, 2002.

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. The draft assessment could be enhanced by considering additional selective quantitative analysis and further evaluation of dose-response relationships, especially of the relative likelihood of the different metabolites to play a role 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.

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.

It is important to base potency estimates, however, of the metabolites resulting from direct exposure versus from TCE metabolism on time-dependent liver dosimetry. 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.

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

1
2 b) TCA is metabolized to DCA yet the liver tumors induced by DCA display
3 different characteristics compared to the tumors induced by TCA (section 3.5.1.2). Was
4 a comparison of these tumor characteristics induced by TCA and DCA ever made to
5 similar tumors produced by TCE? Again, a quantitative discussion of the levels of these
6 metabolites present following administration of the metabolite or the parent TCE would
7 be useful.

8
9 c) Another example of a quantitative analysis suggested by a panel member
10 relates to the peroxisome proliferator hypothesis for the mode of action of TCE and/or its
11 metabolites. For this hypothesis for the mode of action, there should be a reasonably good
12 quantitative correlation between the peroxisome proliferation potency and the apparent
13 carcinogenic potency of TCE and possibly its relevant metabolites across species,
14 genders, etc. From the Bull (2000) report in the state-of-the science papers that TCE
15 induces peroxisome proliferation in rats but not liver tumors, and some other comments
16 there, it appears that the correlation may not be very good. If so, a quantitative
17 comparative analysis will reveal that, and may be a basis to contribute to the
18 understanding of this much-discussed mode of action and whether it is an important
19 contributor to bioassay liver tumor observations.

20
21 Given that the peroxisome proliferator hypothesis is the best defined mode of
22 action mentioned under Bull's discussion of "Modification of Cell-Signaling Pathways,"
23 the Panel does not completely understand the relatively favorable attention given to this
24 possibility in the discussion of the draft assessments. The panel believes the potential
25 mode of action discussion should include this hypothesis in the review. However some
26 panel members suggested that EPA should consider giving it somewhat less weight than
27 the possibility that increases in cell replication rates secondary to high dose toxicity
28 interact with some amount of classical mutagenic/clastogenic activity by highly reactive
29 intermediates such as the TCE-epoxide or metabolites of the metabolites TCA and DCA
30 (see suggestion below that additional quantitative analysis of genotoxic hypotheses be
31 included to the extent possible based on available data). One panelist suggested that the
32 open question of the possible contribution of the release of free TCE-epoxide and
33 resulting DNA reactions be at least mentioned in the revised draft assessment. It also
34 should be noted that the mechanisms by which TCE metabolites affect cell cycling have
35 not been sufficiently worked out so as to provide a clear indication on how these changes
36 in relation to metabolite dosimetry and as a function of age relate to the probability of
37 liver tumor development}

38
39 d) In section 3.5.1.2, the cell-signaling mode of action for TCA and DCA is
40 discussed. The only paper that is cited that supports this mode of action is by Bull (2000).
41 Are there other studies in which this potential mode of action is supported? If so, they
42 should be included. The responses observed for TCA and DCA are not compared
43 specifically to what occurs following doses of TCE that cause observed liver tumors. Are
44 these data available? If not, the Panel advises EPA to present the doses of TCA and DCA
45 administered to cause these responses along with a prediction [utilizing physiologically-

1 based pharmacokinetic (PBPK) models] of the levels of these metabolites that would be
2 formed in the liver following administered dose of the metabolite or TCE.

3
4 e) A more quantitative discussion of the genotoxic data relative to cytotoxicity
5 and tumor formation is especially important in clarifying the genotoxic contributions to
6 carcinogenic action and in understanding the shape of the dose response curve at human
7 exposure levels. The Agency's characterization of TCE and its major metabolites as
8 "weak" mutagens/clastogens in various test systems implies that the observed rather low
9 potency for carcinogenic activity by TCE is somehow not consistent with a primary
10 genetic mode of action because TCE and its metabolites do not have what might be called
11 "strong" potency for mutagenic endpoints. The use of terms such as "weak" and "strong"
12 in this context is vague and open to misinterpretation.

13
14 If arguments of this sort are to be used by the Agency, the Panel advises EPA to
15 base those arguments on quantitative analysis of the correlation between mutagenic
16 potency in specific test systems used for TCE and its metabolites and carcinogenic
17 potencies for chemicals (perhaps related chemicals) as conventionally determined by
18 EPA procedures. The general impression of some panel members is that such
19 correlations, while present, are imprecise enough that they are not likely to support a
20 strong inference that an observation of relatively low mutagenic/clastogenic potency by
21 major TCE metabolites is inconsistent with a genetic mode of action for the relatively
22 low carcinogenic potency of TCE compared with other related small-molecular-weight
23 organic chemical carcinogens.

24
25 Some other comments by panel members suggested various types of summaries to
26 strengthen the draft assessment. In particular,

27
28 a) It would be useful to include a table summarizing evidence for and against the
29 potential modes of action by which TCE causes liver, kidney and lung cancer. This
30 would include which metabolite has been demonstrated or is suspected to operate through
31 which specific mode(s) of action and at what exposure levels.

32
33 b) In discussing the various metabolites and their related reactions, a
34 comprehensive metabolic pathway should be given. There was the mention of Figure 2-1
35 (page 2-1, line 2) in which TCE metabolic pathways and those from chemicals sharing
36 some TCE metabolites were presumably given. However, Figure 2-1 is missing from the
37 draft assessment. This should be rectified. Figure 3-1 on page 3-57 achieved part of that
38 purpose; however, the sharing of part of the metabolic pathway by other chemicals
39 should be explicitly indicated.

40
41 A summary sentence or paragraph would often be helpful at the end of long text
42 discussions of alternative hypotheses in order to clarify EPA's overall conclusion about
43 likely modes of action for different metabolites and toxic effects.

44
45 The Panel notes that the current draft assessment, in discussing the effects of
46 metabolic interactions, emphasizes the possibility that these interactions will increase

1 toxicity. This is not necessarily true. Various alternatives should be discussed. Since it is
2 commonly accepted that TCE metabolites are the more toxic species, the overall TCE
3 toxicity might decrease to the extent that this would lead to some increase in the
4 exhalation or urinary excretion of unchanged TCE. On the other hand, if TCE
5 concentration increases in the blood because the P450 pathways are partially saturated,
6 the amount of TCE processed via the GST pathway would be expected to increase,
7 leading to greater internal exposure to renal toxic metabolites. The Panel advises the
8 Agency to evaluate where evidence exists regarding such competitive inhibition of TCE.

9
10 The Panel also notes that, although the draft assessment did a very good job of
11 exploring different pathways, there may have been too great a tendency to focus on the
12 individual actions of particular metabolites, in part because key informative experiments
13 have most often been done by administering either TCE itself or specific metabolites by
14 themselves. The draft assessment, however, does usefully note that no one metabolite
15 may be totally responsible for specific toxic actions. Therefore there should be
16 continuing research both on pharmacokinetic and pharmacodynamic interactions between
17 TCE, TCE metabolites and possibly other environmental toxicants.

18
19 The Panel recognizes that, given the current state of knowledge, there is
20 uncertainty in which metabolites cause specific adverse effects and in the sequence of
21 biological changes that lead to tumor development. Consequently, it is recognized that
22 there would be substantial uncertainties associated with extrapolations of hypothetical
23 mechanisms (or modes of action hypotheses) across species.

24
25 In conclusion, the Panel reiterates its commendation of EPA for an extensive
26 evaluation of different modes of actions in the current document. However, the Panel
27 strongly advises the Agency to add a more thorough quantitative evaluation of dose
28 response relationships and dosimetry to its discussion of the role of different metabolites
29 and multiple modes of action. Quantitative data are available in the literature that can
30 improve characterization of mode of action in terms of cross-species and low dose
31 extrapolation. More extensive use of this information can improve scientific
32 understanding and strengthen the basis for decisions on cancer classification and the final
33 risk assessment approach.

1 4. CHARGE QUESTION 2

2
3 4.1. Agency Charge Question and Suggested Areas for Inquiry

4
5 Charge Question: Is the cancer weight-of-evidence characterization adequately
6 supported?

7
8 Suggested Areas for Inquiry: The cancer characterization is based on both
9 epidemiological and animal studies. Does the draft assessment adequately characterize
10 the strength of the epidemiologic evidence and adequately address questions concerning
11 the analysis by Wartenberg et al. (EHP 2000) and its inclusion of the Henschler study?
12 Does the draft assessment adequately present and consider the animal evidence of tumors
13 at multiple sites and its relevance to humans?

14
15 4.2. Panel Response

16
17 The Panel agreed that the cancer weight-of-evidence characterization is
18 adequately supported. Members of the Panel commended EPA for compiling such an
19 extensive array of scientific literature including over 80 epidemiological studies and
20 hundreds of toxicological and mechanistic studies, and summarizing the evidence
21 relatively clearly and cohesively. The panel endorsed EPA's use of a combination of
22 human epidemiological studies, animal toxicology studies, and mechanistic data to make
23 a cancer risk determination.

24
25 The Panel agreed that the Agency's overall qualitative cancer risk determination
26 is reasonable based on: a) significant experimental evidence showing tumors at multiple
27 sites in two species (rats and mice); b) epidemiologic evidence in humans showing
28 associations between TCE exposure and several cancers including at several of the same
29 sites seen in animal bioassays; and c) mechanistic data indicating relevance of
30 experimental findings to humans. One panel member suggested that EPA clarify more
31 explicitly for the public what is meant by a "weight-of-evidence characterization." Panel
32 members differed in their interpretation of how to apply the draft revised cancer
33 classification guidelines and some requested clarification of the EPA cancer guidelines
34 classification scheme before they could form a personal opinion. Several panel members
35 characterized the weight of evidence as "very strong" and spoke in support of the
36 Agency's proposed designation of TCE as "highly likely to be carcinogenic to humans,"
37 Several members, however, also suggested that the chemical could come closer to being
38 classified as "known to be carcinogenic to humans."

39
40 4.2.1. Human Epidemiological Studies

41
42 Among the epidemiological studies, the data appear strongest overall for liver
43 cancer and also, to some degree, for lymphoma. All Tier 1 studies showed excesses of
44 liver cancer. There was a request for more data on exposure-response relationships for
45 liver cancer from the Tier 1 studies, and for more discussion of the liver cancer endpoint
46 generally, since it was felt to be so strong. Tier 1 studies show excesses for Hodgkin's

1 disease, non-Hodgkin's lymphoma, and multiple myeloma. The addition of a recently
2 published study by Hansen et al., significantly adds to the weight of evidence for
3 lymphoid tumors.

4
5 The Panel did have some concerns about the strength of the evidence for the
6 kidney cancer endpoint based on the available epidemiological data. The uncertainty
7 focused primarily on the study by Henschler et al. Concerns included: a) this study
8 originated as a cluster investigation, thereby potentially introducing bias; b) the
9 variability of underlying population rates for kidney cancer in German and Danish cancer
10 registries; c) the magnitude of the indicated risk which was far out of proportion to risks
11 observed in most other studies; and d) the significance of the Henschler study in light of
12 the whole epidemiology database.¹

13
14 There was agreement that the inclusion of the Henschler study introduces
15 significant heterogeneity onto the overall meta-analysis of the renal cancer endpoint. In
16 addition, the Panel noted that Henschler study did not report any excess in liver cancer,
17 thereby making the study less credible in light of the rest of the epidemiological
18 literature. In defense of the Henschler study, several panel members raised the following
19 points: a) in Germany, people frequently remain in the same workplace for many
20 decades, thereby potentially increasing the total lifetime exposure in this cohort; b) from
21 the description of the workplace, the exposures may have been very high compared to
22 other studies; c) the results were consistent with the Vamvakis study (1998), somewhat
23 consistent with the recently published study by Pesch et al., and in line with the animal
24 toxicology and mechanistic data (including the apparent over 10-fold increased risk
25 reported among exposed workers with inactive forms of two GST genes) (Brüning et al,
26 1997a); and d) the very high TCE exposure may saturate P450 pathways thereby
27 shunting the TCE toward the GST pathway and if that is the case, it is likely that kidney
28 tumor may predominate.

29
30 Some members pointed to the history of cancer clusters in identifying other
31 significant occupational carcinogens (e.g. asbestos bis-chloromethyl ether, vinyl
32 chloride). In these instances, the increased incidence in tumors associated with these
33 other chemicals in one epidemiological study was replicated in other epidemiology
34 studies. In the end, despite the uniqueness of the Henschler study, the panel generally did
35 not advocate omitting it from the draft assessment.

36

¹ 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 cohort screening using abdominal sonography which should yield a higher incidence of tumor than expected from a population based cancer registry.

1 Several panel members said that the Henschler study should be omitted from
2 consideration only if it were to become fairly clear that there is some other factor that
3 would explain the elevated incidence and mortality from renal cancer in this cohort. In
4 that case, the Agency could use the Finnish and Danish studies with liver and lymphoma
5 as end points, and then simply discuss kidney, prostate and cervix without quantification
6 of risk. The Panel recommended EPA to include this study in the overall weight-of-
7 evidence, taking into account information on exposure levels, and to re-evaluate whether
8 the Henschler study fits the criteria for a Tier 1 study and discuss the results in light of
9 competing lines of evidence including the recently published Danish study.

10
11 Panel members endorsed the division of the cohort studies into three tiers, and
12 recommended that EPA explicitly weight the Tier 1 cohort studies (and case control
13 studies that specifically focus on TCE) more strongly than the other studies that involved
14 exposure to a variety of chemicals. The Bradford-Hill criteria for establishing causality
15 are a useful yardstick for determining the comparative strengths of different studies.
16 Although there was some debate about the relevance of the Tier 3 dry cleaner/laundry
17 worker studies, there was support for continuing to include these studies because many of
18 the metabolites of PCE and TCE are the same. These dry cleaner studies, however,
19 should not be weighted heavily in the overall weight-of-evidence assessment.

20
21 Several members suggested including discussions about prostate cancer and
22 childhood leukemia, as there is limited epidemiological evidence to support both of these
23 endpoints. In the case of prostate cancer, all the Tier 1 cohort studies showed slight
24 increases in relative risk, leading to questions about a possible weak tumorigenic effect in
25 humans. In the case of childhood leukemia, this disease has shown up in numerous
26 community-based studies. In case control studies of childhood leukemia, parental
27 occupation in a solvent-exposed industry is a consistent positive association (although the
28 link specifically with TCE is unclear). Childhood leukemia would not be expected to
29 show up in the occupational cohort studies because these studies did not evaluate
30 offspring. In addition, the Panel recommended that EPA add a discussion of the Hansen
31 (2001) study, which adds scientific weight to the lymphoma and cervical cancer
32 endpoints, but not to the kidney cancers, and of the recent Pesch study that found a
33 slightly increased risk of kidney cancers. There was also a recommendation for a
34 discussion in this section of glutathion S-transferase (GST) polymorphisms and their
35 possible role in creating susceptible subpopulations for kidney cancer (Brüning et al.,
36 1997).

37
38 Some panel members had criticisms and concerns about the Wartenberg review
39 article (2000). In particular, the following points were raised: a) Wartenberg et al.
40 adjusted the lower bounds of the confidence intervals of the reviewed studies, such an
41 adjustment can be misleading and lead to results that appear to be more significant than
42 they are (If the results need to be symmetrical on the log scale, the upper confidence
43 bound could be lowered instead, or the confidence intervals could simply have been
44 presented as published by the original authors without impeding the ability to calculate
45 the variance of the log of the SMR); b) the Wartenberg review included blanks (dashes in
46 the tables) for some endpoints where no cases occurred in the original studies even

1 though some were expected, this could bias the overall analysis toward finding an effect;
2 c) in at least one case (Henschler brain tumors), risk numbers for the exposed group were
3 reported even though the risks in the unexposed group in the same study were actually
4 higher; and d) the separate calculations of incidence and mortality resulted in some
5 cancers being counted twice, once in the incidence summary statistics, and again in the
6 mortality summary statistics.

7
8 The Panel agreed that some of the key underlying studies need to be directly
9 examined by the Agency and potential biases and errors should be addressed and
10 corrected. Although epidemiology is a relatively insensitive science and is not good at
11 detecting risks that are small in relative risk terms, it may be potentially important in
12 terms of population-attributable risk. In that context, the burden is on EPA to make
13 decisions about which studies to weight most heavily with an eye toward justifying the
14 decisions scientifically and protecting the public health.

15
16 There was a discussion of the pros and cons of performing a formal meta-analysis
17 of the TCE cancer studies. While several panel members advocated a more traditional
18 meta-analysis of the Tier 1 studies, others pointed out that the study designs were perhaps
19 too disparate, and that a meta-analysis would simply demonstrate a lot of uncertainty and
20 would add very little information. The Panel advises the Agency to use the Bradford-Hill
21 criteria in weighing the overall epidemiological evidence and to provide tables
22 summarizing critical information for each key epidemiology study including type of
23 study, number of subjects, sources of exposure information, years and estimated levels of
24 exposure, and basis for the estimated exposure levels.

25 26 4.2.2. Animal Toxicology

27
28 The panel agreed that TCE is an animal carcinogen, although its potency is
29 relatively weak. Tumors are observed in multiple organs of multiple strains of two
30 species at relatively high doses. In the rat, TCE has been observed to cause a low
31 incidence of rare kidney tumors at high doses (in the presence of renal toxicity), which
32 should be considered treatment-related. TCE also causes Leydig cell tumors in the male
33 rat, another effect that is likely to be treatment-related. In the mouse, liver tumors
34 occurred primarily by gavage rather than by inhalation, and these are considered to be
35 treatment related, as are the lung tumors after exposure by the inhalation route.

36
37 Lymphomas in the mouse are more problematic; these were increased in 3/6
38 studies, but may only be treatment-related in one study, because the NTP study showed
39 the incidence in the treatment group fell within the range of historical controls. There was
40 a suggestion that EPA reexamine the mouse lymphoma data to see if the endpoint is
41 treatment-related. If EPA decides the mouse lymphoma endpoint is treatment-related,
42 then a discussion reflecting the issues with the NTP studies should be added. In general,
43 many of the carcinogenicity studies that were considered negative are not included in the
44 tables and all studies for each tumor type should be included. In terms of site
45 concordance, none of the tumors observed in rats were observed in mice and vice-versa.

46

1 There was discussion about the genotoxicity issue with multiple viewpoints
2 expressed on the likelihood of genotoxicity. It was the general consensus of the panel that
3 genotoxic mechanisms can not be completely ruled out.
4

5 Some panel members supported the conclusions concerning the genotoxicity of
6 TCE and its metabolites, as discussed by Moore and Harrington-Brock (2000). They
7 concluded: "the weight of evidence argues that chemically induced mutation is unlikely
8 to be a key event in the induction of human tumors that might be caused by TCE or its
9 metabolites. This conclusion draws from the fact that these chemicals require very high
10 doses to be genotoxic. The exception is DCVC, the glutathione conjugate of TCE.
11 Moore and Harrington-Brock (2000, Page 221 1st paragraph) conclude that the potency of
12 DCVC is unknown "because there are no data for mammalian cells from in vitro or in
13 vivo experiments. Thus, while the weight of evidence indicates that most of the tumors
14 induced by TCE are unlikely to be due to a mutation event, it is not possible to exclude
15 this possibility.
16

17 One different view expressed, however, was that the draft assessment fails to
18 reflect the weight of evidence that TCE is unlikely to be genotoxic (except in the case of
19 the kidney cancers where there is more evidence for genotoxicity). The draft assessment
20 states that TCE and its metabolites are "poor genotoxicants," or "weak genotoxicants."
21 The draft assessment notes that there are some differences in the mutation spectra for
22 TCE, DCA and TCA, that mutations only are observed at high doses, and that the effects
23 of DCA may be more important than TCA, but probably both are involved. The draft
24 assessment notes that DNA damage may not be as important at lower exposures as effects
25 on gene expression. Also, some effects on DNA methylation are discussed. Another
26 view expressed was that the genotoxic hypothesis needs to be more carefully and
27 quantitatively examined by the methodology described in the response to Question 1.
28 Panel members, overall, somewhat different views on the weight that should be given to
29 genotoxic modes of action for the liver tumors. It would be prudent to keep evaluation of
30 the genotoxic hypothesis in the mix of possibilities until it is more convincingly
31 evaluated with a quantitative comparative potency analysis.
32

33 Other panel members were concerned about the remaining possibility of
34 genotoxicity. One panel member raised the issue of a transient epoxide intermediate that
35 may be formed in the first metabolic step in the oxidative pathway because the oxidative
36 metabolites TCA and DCA are derived from this intermediate. There is some evidence
37 that this may occur, and the issue is discussed in the Lash paper (2000), but this issue is
38 not even mentioned in the EPA draft assessment. Another panel member raised the issue
39 of the mutagenicity of chloral hydrate as another controversy that bears more discussion
40 in the draft assessment. Several panel members advocated strengthening the discussion of
41 genotoxicity in the draft assessment.
42

43 Another view expressed was that the genotoxic hypothesis needed to be more
44 carefully and quantitatively examined by the methodology described in the response to
45 Question 1. Panel members overall, held somewhat different views on the weight that
46 should be given to genotoxic modes of action for the liver tumors. It would be prudent to

1 keep evaluation of the genotoxic hypothesis in the mix of possibilities until it is more
2 convincingly evaluated with a quantitative comparative potency analysis.

3
4 For liver tumors, several hypotheses are discussed in the EPA draft assessment,
5 including: peroxisome proliferation, disturbances in cell signaling and carbohydrate
6 metabolism, and DNA damage. TCA and DCA likely account for the liver tumor
7 response to TCE, but have different characteristics. TCA is more potent than DCA and
8 has a greater sustained peroxisome proliferation effect. TCA and DCA when given
9 individually, result in tumors that are phenotypically different. An explanation is that
10 DCA and TCA may selectively modify the growth rates of different clones of cells via
11 altered cell replication and apoptosis rates. Many scientists agree that TCA and DCA are
12 hepatic tumor promoters (a term that is avoided in the risk assessment draft assessment)
13 that exert their effects through cell proliferation and death. Different tumor promoters
14 select different subpopulations of hepatocytes that are clonally expanded. In the risk
15 assessment draft assessment, there is considerable discussion of effects of TCE and its
16 metabolites on carbohydrate metabolism. One panel member viewed this discussion as
17 speculative, and felt that the significance of this mode of action is not really clear. One of
18 the problems with DCA is that it is not measurable after the administration of TCE, but
19 modeling studies indicate that there is sufficient exposure. The conclusion is that both
20 TCA and DCA contribute to the hepatocarcinogenicity of TCE in mice at high dose
21 levels and that chloral may also be involved.

22
23 For rat kidney cancers, there was agreement that the draft assessment
24 characterized alternative modes of actions. There were differences among panel
25 members about whether the scientific evidence was sufficiently strong to support a mode
26 of action for kidney tumor formation based on the GST metabolite. Some panel members
27 believed that the mode of action of the kidney cancers was likely to be primarily through
28 the GST metabolite, DCVC, a known mutagen and cytotoxic chemical, and that this
29 mode of action was relevant to humans. In this view, peroxisome proliferation and alpha
30 2u-globulin were unlikely modes of action in the kidney. From this perspective, the
31 cytotoxic and mutagenic potential of DCVC following its activation by renal beta-lyase,
32 both modes of action was potentially involved in the mode of action for kidney tumors.
33 The finding of DCVC in blood of human volunteers exposed to TCE and the presence of
34 beta-lyase in the human kidney provided additional evidence that the GSH-mediated
35 pathway was operable in humans.

1 An alternate view on the panel was that the EPA document did not include critical
2 information to fully characterize the weight of evidence for kidney tumor formation in
3 rats. Information that would be helpful would include the extent of kidney toxicity and
4 mortality observed at dose levels causing the low incidence of kidney tumors and the
5 dose-response relationship of TCE and key metabolites relevant to the different modes of
6 action. More detailed discussion of the deficiencies observed can be found in the
7 footnote below.²

8
9 There was agreement that EPA adequately captured the scientific issues regarding
10 mouse lung tumors. It is postulated that this is due to the formation and accumulation in
11 the Clara cells of Chloral Hydrate (CH) formed via CYP2E1. CYP2E1 and Clara cells
12 are higher in mice as compared to rats and humans suggesting a species-specific mode of
13 action. The draft assessment states that this hypothesis requires further investigation and
14 also states that CH is clearly clastogenic and mutagenic at high doses, suggesting that
15 both genotoxicity and cytotoxicity may be involved. There is debate about the relevance
16 to humans of the rat Leydig cell tumors, which might be expanded and improved by a
17 fuller discussion, including a discussion of rat Leydig cell tumors in the draft assessment,
18 with a reference to the paper by Cook et al., which argues that these tumors are not
19 relevant to humans

20
21 The overall toxicological assessment was that the rat kidney cancers are relevant
22 to humans. There was some scientific difference of opinion about the human relevance at
23 low doses of the lung and Leydig cells. Regarding the mode of action, panel members
24 agreed that a genotoxic mode of action cannot be excluded for kidney tumor formation
25 based on the currently available evidence, although there was a difference of opinion
26 about the likelihood that a genotoxic mode of action exists for TCE. Overall, the Panel
27 recommended that EPA expand the discussions about some of the main scientific
28 controversies, with some more references to the primary scientific literature in selected
29 cases involving critical studies.

30
² Although the draft assessment dismisses peroxisome proliferation as an unlikely mode of action, it did not provide the critical analysis provided by Lash et al. (2000) that states that the central issues are a) whether significant formation of TCA and DCA occurs in the kidneys, b) whether peroxisome proliferation is induced to a significant extent in the renal proximal tubules, and c) whether this mechanism occurs in humans. Thus, even though the one direct experiment studying effect of TCE on peroxisome proliferation actually caused increase in palmitoyl-CoA oxidation activity in liver and kidney of both mouse and rat, Lash concluded that peroxisome proliferation was an unlikely mode of action relevant to humans based on inferences regarding internal dosimetry of TCA in kidneys and because, in general, renal peroxisomes are generally less responsive to peroxisome proliferators than hepatic peroxisomes and because peroxisome proliferation is less relevant to humans.

Likewise, the discussion on DCVC and DCVG needs to include the evidence on whether significant formation of DCVC and DCVG is likely to occur in the kidneys at human exposure levels and better characterization of the genotoxicity (e.g. only at cytotoxic levels? only in vitro bacterial systems?) Without this type of more rigorous scientific discussion, it is not possible to determine if DCVC and DCVG is an MOA that is relevant to humans. Lash et al. (2000) acknowledges that there is a need to better understand quantitatively if “enough of the reactive metabolite generated from DCVC is produced at typical exposure doses of TCE.”

1 5. CHARGE QUESTION 3

2
3 5.1. Agency Charge Question and Suggested Areas for Inquiry

4
5 Charge Question: A new feature of the cancer database is molecular information
6 on the von Hippel-Lindau (VHL) tumor suppressor gene. Is this information adequately
7 discussed and are the conclusions appropriate?

8
9 Suggested Areas for Inquiry: Does the draft assessment adequately present
10 alternative interpretations of the von Hippel-Lindau findings and identify this as a
11 research area that would help resolve an open question about TCE and kidney cancer?

12
13 5.2. Panel Response

14
15 The consensus of the panel is that the discussion in the draft assessment is
16 generally appropriate. There was a recommendation to strengthen the description from
17 the "suggestive evidence" referred to on line 8 of page 3-38. The panel generally agreed
18 that EPA is wise not to regard the evidence as entirely conclusive pending independent
19 confirmation by another group. The discussion in the draft assessment might be
20 improved by including some additional comparative observations from kidney cancers
21 not in the TCE exposed workers. Panel members offered the following enhanced
22 discussion as a starting point for EPA consideration.

23
24 Mutations in the VHL tumor suppressor gene (both germline and somatic) have
25 been associated with increased risk of renal cell carcinoma (RCC). Recent studies by
26 Bruning et al. (1997) and Brauch et al. (1999) provide evidence that TCE exposure may
27 be associated with VHL mutations among RCC patients. Specifically, Bruning et al.
28 examined VHL mutation by Single Strand Chain Polymerization (SSCP) in renal tissue,
29 initially from 23 RCC patients with documented high occupational TCE exposure. All
30 (100%) of this first set evidenced VHL mutation, which the authors concluded was higher
31 than the background frequency of 33% - 55% among TCE-unexposed RCC patients. In a
32 follow-up, Brauch et al. determined VHL mutation frequencies by SSCP and direct
33 sequencing of mutations in renal tissue from 44 TCE-exposed RCC patients. 75% of
34 TCE-exposed patients had mutations in VHL and 39% had a "C to T" mutation at
35 nucleotide 454. (All C>T transitions in the control renal cell carcinoma patients were
36 evidently relatively rare at about 6% total incidence based on combined data from several
37 authors.) VHL mutations were detected by Baruch et al. in workers with medium and
38 high but not low TCE exposure. However, only 3 patients were classified as having low
39 exposure. Overall, these data indicate a highly significant association ($p=0.0006$) between
40 TCE exposure and multiplicity of VHL mutations.

41
42 The authors of this paper did not measure total VHL mutation frequency among
43 TCE-unexposed RCC patients, but used a restriction endonuclease-based assay to
44 evaluate the specific "C to T" mutation at nucleotide 454 among 107 unexposed patients.
45 None of the TCE-unexposed RCC patient had the "C to T" mutation at nucleotide 454,
46 indicating a mutational hot spot in VHL associated with TCE-exposure. The apparent

1 elevation in the frequency of renal cancers with this specific mutation is indicated to be at
2 least six-fold, and is likely to be 40 fold or more.

3
4 Applying a Poisson distribution to the occurrence of this specific mutation in the
5 studied groups, the finding of zero cases in 42 VHL mutation bearing tumors in the
6 control group can be used to rule out a true incidence of as much as three cases in 42 (or
7 about seven percent) with 95% confidence. Therefore a conservative estimate of the
8 relative enhancement of the frequency of this specific mutation in the renal cancers from
9 the trichloroethylene exposed workers is $39\%/7\% = 6$ fold. If we take as a plausible but
10 very tentative “best estimate” incidence of 0.5 of these mutations in 42 mutation-bearing
11 controls examined (about 1%), then the indicated enrichment of the specific mutation is
12 about $39\%/1\% =$ just under 40 fold. The true enhancement could of course be even
13 larger than this, but that could only be determined by observations with a much larger
14 sample size.

15
16 Follow-up studies are needed to confirm the association between TCE and
17 mutations at nucleotide 454 and to compare total mutation frequencies in VHL gene
18 among RCC patients with and without TCE exposure, as there is uncertainty over the
19 background rate of VHL mutations in RCC. Nonetheless, the Agency’s conclusion that
20 these findings appreciably “augment” the characterization of TCE as highly likely to
21 produce cancer in humans (3-51) is appropriate.

22
23 The importance of these observations is reinforced by finding an association of
24 the VHL mutations with loss of heterozygosity at the VHL locus (Baruch et al., 1999)—
25 making a strong analogy with the classic case of changes in both copies of the
26 retinoblastoma gene in the causation of retinoblastoma. If the hot-spot and other VHL
27 mutations found in the worker studies are in fact inactivating mutations coupled with loss
28 of heterozygosity indicating inactivation of the homologous VHL gene on the opposite
29 chromosome, then the inference must be that these mutations are not just indicators of
30 TCE exposure, but are likely to be directly on the causal pathway for the kidney cancers.
31 The Panel suggests that EPA address this issue in the draft assessment.

32
33 Another suggestion for the Agency to consider is that the discussion could be
34 improved by more clearly defining the “alternative” hypothesis (lines 26-28 on p. 3-38)
35 about some selection mechanism that could account for these observations without
36 involving mutagenesis by a TCE metabolite. Certainly it is conceivable that the overtly
37 toxic conditions of high level TCE exposure could lead to differential growth vs.
38 death/differentiation rates for cells with particular mutations. But the mutations must be
39 present in the cell population in order to be selected.

40
41 To date there is no supplementary information on the implications of this
42 particular mutation (other than probably repressing VHL gene function—which is likely
43 to be a property of many other tumor-associated mutations as well) that supports the idea
44 that cells possessing this mutation would have a selective advantage over cells possessing
45 other VHL-inactivating mutations. The most likely alternative hypothesis is that
46 somehow cells with this particular VHL mutation have an enhanced selective advantage

1 in the TCE-influenced kidney environment before the final mutagenic steps leading to
2 fully developed tumors have occurred. The differential selective advantage might lead to
3 a larger clone of precursor cells (relative to precursor cells with other VHL mutations) in
4 which the final mutagenic steps leading to cancer can occur.

1 6. CHARGE QUESTION 4

2
3 6.1. Agency Charge Question and Suggested Areas for Inquiry

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

9
10 Suggested Areas for Inquiry: The RfD and RfC were developed after considering
11 both human and animal studies. Does the draft assessment adequately characterize the
12 data at each site of toxicity and focus on an appropriate subset of critical effects? A key
13 issue is the application of uncertainty factors. Alternative views range from use of fewer
14 uncertainty factors to use of additional uncertainty factors to reflect studies showing
15 reproductive effects and enzyme differences between children and adults. Does the draft
16 assessment adequately discuss and characterize the evidence supporting alternative
17 positions as it arrives at an RfD and RfC?

18
19 6.2. Panel Response

20
21 6.2.1. Multiple Critical Effects: Does the draft assessment adequately characterize the
22 data at each site of toxicity and focus on an appropriate subset of critical effects?

23
24 The draft assessment summarizes many epidemiological and experimental studies
25 and identifies the Lowest-observed-adverse-effect levels (LOAELs)/ no-observed-
26 adverse-effect levels NOAELs for multiple critical effects to aid in development of a
27 single point of departure. The Agency's consideration of multiple noncancer endpoints in
28 both the general discussion and in the derivation of the RfD and RfC is commendable.
29 TCE clearly has important hepatotoxic, nephrotoxic, neurotoxic, immunologic,
30 developmental and reproductive effects that should be considered in the derivation of the
31 RfD and RfC. The use of multiple critical effects increases one's confidence that the
32 point of departure dose is at the low end of doses at which adverse effects can be
33 observed.

34
35 Some Panel members suggested that the characterization of the data at each site of
36 toxicity could be strengthened considerably. The Panel recognizes that a lengthy
37 dissertation of each study cited by EPA would be counterproductive. However, in the
38 opinion of some panelists, the current discussion lacks the type of critical analysis and
39 discussion of the weight of evidence that is necessary to understand the Agency's
40 rationale for selection of endpoints, level of concern, dose-response extrapolation, effect
41 of time-duration on key endpoints, and application of uncertainty factors. Other panel
42 members thought the discussion of non-cancer effects and discussions surrounding the
43 development of the RfD and RfC were quite good and that with relatively limited
44 additional clarification the non-cancer section of the Draft Assessment would be
45 complete.

46

1 The general recommendations for improvement of Section 3.4. of the draft
2 assessment are identified immediately below. Detailed comments on specific endpoints
3 that are important for EPA to consider can be found in Appendix B to this report.
4

5 a) The Panel advises the Agency to discuss the key studies in Section 4 and listed
6 in Table 4.2 in greater detail to outline the scientific basis for selection of endpoints for
7 derivation of the RfD and RfC. At present, some of the critical studies in section table
8 4.2 that are used to derive the RfD/RfC are not discussed at all in section 3.4; others are
9 given only a cursory mention. This is a striking deficiency in the draft assessment
10 prevents EPA's rationale for deriving the RfC and RfD from being clearly understood.
11

12 b) The discussion of the specific toxicity endpoints in section 3.4 does not provide
13 the essential information that is necessary to understand the Agency's rationale for
14 selection of point of departure, level of concern, or uncertainty factors. Although a
15 lengthy detailed dissertation of the different studies is not appropriate, a more critical
16 evaluation of the data is needed. At a minimum, scientific data such as exposure levels,
17 severity and nature of effects, methods used to detect effects would be useful. The Panel
18 suggests that EPA include tables of studies discussed for each organ toxicity discussion.
19 These tables could include information on species, number of subjects/animals, doses
20 used, route and duration of exposure, type of effect noted at each dose. Additional
21 information useful for human studies includes type of study (e.g. cohort, case control,
22 cross sectional, ecologic, prevalence), source of control population, method of
23 establishing exposure levels, and possible exposures to other chemicals. Finally,
24 discussion of data, especially pharmacokinetic and pharmacodynamic data that assist in
25 understanding relative sensitivity of humans and animals and in understanding responses
26 relative to duration of exposure could be highlighted in order to provide a stronger
27 scientific foundation for later discussions on uncertainty factors. This type of balanced
28 critical evaluation would strengthen the scientific data necessary to support the Agency's
29 derivation of the RfD and RfC.
30

31 c) An improved critical analysis and discussion (as outlined in point 2) of key
32 developmental studies and other studies evaluating different life-stages should be
33 integrated into each toxicity section. It will be important to highlight any data and
34 relevant mechanistic data that will aid in understanding relative sensitivity of different
35 life-stages. These discussions will then provide a strong scientific basis for a separate
36 section devoted to summarizing and integrating discussion of the different developmental
37 effects.
38

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

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

9
10 f) The Panel advises EPA to develop its assessment from the set of well-
11 conducted studies that make a difference to the weight of evidence. Evaluation of the
12 quality of the study using criteria developed by EPA for adequacy of studies is especially
13 important to understand the strengths and weaknesses of different papers cited (EPA
14 Draft RFD/RfC process, May 2002, page 4-6 to 4-8). Additional studies that should be
15 integrated into the critical evaluation of the weight of evidence are by Fisher et al. (2001)
16 and Albee, R. (1993, 1994). Any other well-conducted studies on TCE, especially those
17 conducted under Good Laboratory Practices that have been submitted to EPA need to be
18 evaluated by these criteria.

19
20 The Panel is providing these general comments as major areas that should be
21 addressed for each of the noncancer endpoints. Specific comments on noncancer
22 endpoints are provided in Appendix B to this report. Section 1 of Appendix B addresses
23 the EPA's question: Does the draft assessment adequately characterize the data at each
24 site of toxicity?

25 26 6.2.2. Modes of Action of TCE Toxicity

27
28 The mode-of-action discussion in the draft assessment focuses on cancer.
29 However, the discussion is also important to the non-cancer toxicity. The draft
30 assessment needs to provide a balanced discussion of the role of TCE and metabolites in
31 the mode of action of TCE toxicity. Bull (2000) concluded that DCA is unlikely to
32 contribute to the induction of peroxisome synthesis at levels that are produced by the
33 metabolism of TCE. Barton and Clewell (2000) conclude that there are two major
34 hypotheses for the mode of action of TCE in the causation of neurological effects: the
35 activity of parent TCE, or the metabolite, TCOH. In their opinion, DCA is not considered
36 to play a role. While some panelists believe the role of DCA in non-cancer endpoints
37 such as neurotoxicity is overstated in the draft assessment, given these conclusions of the
38 state-of-the-science papers, others were not convinced that the state-of-the-science papers
39 are correct on this point and found it reasonable for EPA to consider studies involving
40 DCA. In addition, the discussion of TCE metabolism needs to include the impact of
41 exposure levels on the kinetics of TCE metabolism and compare and contrast what is
42 known about the kinetics at the high doses studied, compared to environmentally relevant
43 levels.

44 45 6.2.3. Uncertainty Factors - Areas of Agreement and Differences Within the Panel

46

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

5
6 The Panel advises the Agency to explain more clearly in the draft assessment how
7 uncertainty factors were derived for the RfD and RfC. The draft assessment does not
8 adequately discuss and characterize the evidence supporting alternative positions in
9 deriving these values. The assessment should address the public comments from the
10 authors of the state-of-the-science papers regarding these alternative positions.

11
12 The Panel also agreed that discussion of uncertainty factors in the document is
13 complex. Multiple factors were chosen by the Agency for the RfD and the RfC, and
14 several charge questions were posed to the Panel related to these factors. The Agency's
15 draft factors and related charge questions are summarized in the table below.

1
 2
 3
 4
 5
 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
Animal-to-Human Uncertainty	10 ⁻⁵	No factor used	Question 4; Section 4 and Appendix B
Subchronic-to-Chronic uncertainty	10 ⁻⁵	10	Question 4; Section 4 and Appendix B
LOAEL to NOAEL uncertainty	10 ⁻⁵	10	Question 4 Section 4 and Appendix B
Other Factors ³	10 ⁻⁵	No factor used	Question 7; Section 9
Children's Safety Factor			Question 9; Section 11
Composite Uncertainty Factor	3,000	1,000	

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 17
 As the Table notes, several Charge Questions, and therefore several parts of this document relate to the issue of uncertainty. The Panel found 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 noted 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.

18
 19
 20
 21
 22
 23
 24
 25
 26
 27
 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.

³ 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.

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

5
6 Several panelists expressed two overall concerns about the uncertainty factors
7 used for the RfD. First, panelists were concerned that children's susceptibility was not
8 included explicitly in the derivation of the uncertainty factors. These panelists felt that it
9 made no sense to include in the document a discussion of ways that fetuses and children
10 are more susceptible to TCE and then fail to account for this susceptibility quantitatively.
11 Secondly, several panelists expressed concern about the fact that EPA actually derived a
12 composite uncertainty factor for the RfD of 5,000, but arbitrarily reduced the factor to
13 3,000. It was unclear which of the uncertainty factors discussed above was eliminated in
14 order to come up with a total of only 3,000 instead of 5,000, and these Panel members
15 asked that this be clarified in the draft assessment. They considered it unscientific and
16 inconsistent to build a composite uncertainty factor and then arbitrarily decrease it to
17 bring it down below a level that the Agency considers acceptable. These panelists urged
18 the Agency to use the full 5,000-fold uncertainty factor if all the components can be
19 justified.

20
21 An alternative view was expressed by other panelists, who noted that a 3.5-5-fold
22 difference between adults and infants for metabolism of TCE should have been included
23 in the EPA analysis. Given the large uncertainty factor of 3,000 already established for
24 the RfD for TCE, these panelists suggested that this additional 5-fold uncertainty factor
25 should be retained as one part of the existing "other uncertainty factor" (either at the 10^{-5}
26 value for this factor set the draft assessment or another value to be set after reexamination
27 of the supporting information) already allocated in the Agency's draft assessment to
28 reflect "professional assessment of scientific uncertainties not explicitly" covered by
29 other factors used (see additional discussion in Section 11 of this draft report). Another
30 view was the 50-fold human variability uncertainty factor for the RfD was probably large
31 enough that an additional factor for children is unnecessary. However, an additional
32 uncertainty factor for children may be warranted for the RfC, which currently only
33 includes a 10-fold factor for human variability.

34
35 A similar set of alternative views emerged relating to uncertainty factors for
36 background exposures. In light of the prevalence of such background exposures in the
37 general population, some Panel members thought it prudent to apply a modifying factor
38 to the RfD, as proposed in the draft assessment. These Panel members felt that in special
39 cases, where data are available for estimating these co-exposures for all relevant
40 populations, the modifying factor could be omitted. Some panelists agreed with the
41 Agency's argument that, unlike the RfD, the RfC was largely derived from human
42 studies, and thus already incorporated these background exposures (because the study
43 subjects likely had similar background exposures as the general population). Therefore,
44 it was a reasonable argument for not applying the modifying factor.

45

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

11
12 Additional general comments relating to derivation of the RfD and RfC and
13 LOAEL to NOAEL uncertainty for the RfD and RfC follow immediately below.
14 Additional detailed comments with recommendations for improving the Agency's
15 discussion and characterization of the evidence supporting alternative positions for use of
16 uncertainty factors for deriving the RfD and RfC can be found in Appendix B.

17
18 The Panel provides the following general advice to the Agency in its discussion of
19 and development of the RfD and RfC in a revised assessment for TCE.

20
21 a) The Panel advises EPA to clarify more fully the reasons for the differences in
22 the uncertainty factors used in the RfD and for the RfC.

23
24 b) In the opinion of some panelists, EPA departed from common practice in
25 applying uncertainty factors from one critical endpoint to an RfD and RfC based on other
26 endpoints. Several members of the Panel expressed strong disagreement with EPA's
27 approach and recommended instead the approach used by Barton and Clewell (2000),
28 which considers each critical endpoint and applied uncertainty factors based on scientific
29 knowledge of the mode of action for that endpoint. This approach would allow the RfD to
30 be supported by all the available data, and in a transparent manner.

31
32 Several other panelists felt that the Agency's approach was justified on the basis
33 of the currently available scientific evidence and for the purpose of ensuring adequate
34 protection. They noted that one would not necessarily expect that all non-cancer health
35 effects would occur at similar doses. In fact, normally some of the effects would be high
36 dose, and one or two might occur at lower doses.

37
38 The Panel agreed, however, to advise EPA to describe explicitly all assumptions
39 about alternative mechanisms when choosing uncertainty factors based on knowledge of
40 mode of action.

41
42 c) Uncertainty Factors for NOAELS and LOAELS. In regard to presentation and
43 communication of the Agency's justification for choosing NOAELS and LOAELS, the
44 Panel advises EPA to show step-by-step how NOAELS and LOAELS of the key studies
45 were converted to human equivalent doses. The Panel advises the Agency to clearly
46 articulate the scientific rationale for selecting the key studies. This is especially needed

1 because these studies are not standard toxicity studies of duration and design that are
2 typically used to set chronic RfDs and RfCs. Such a discussion would make the selection
3 of the point of departure more transparent.

4
5 Improved tabulation of studies in Table 4.2. of the draft assessment, as described
6 in Appendix B, Section 2.4. will go a long way towards making the EPA's decisions
7 more transparent and help the EPA identify areas that require further discussion in the
8 text.

9
10 In regard to the Agency's choice of NOAELs and LOAELs, the Panel represented
11 a spectrum of scientific views about: 1) whether an uncertainty factor for a LOAEL is
12 needed; 2) the size of the uncertainty factor chosen; 3) the rationale for a difference in
13 factors chosen for the RfD and RfC; and 4) why a benchmark dose approach was not
14 adopted, even though it would have reduced uncertainty, not required more uncertainty to
15 be added. These issues and views are discussed in Section 2.4 of Appendix B. The
16 Panel advises the Agency to provide a clearer discussion in the assessment of the
17 spectrum of scientific views on these issues and a clearer justification for the decision
18 made by the Agency.

19
20 There was, however, general agreement that if EPA decides to retain the
21 uncertainty factors described for TCE in the draft assessment, it is important for EPA to
22 spend the time and effort to develop the scientific rationale for these additional factors, so
23 that this new approach is not regarded as arbitrary. For example, the available scientific
24 data on toxicokinetics may help to quantify the impact of background exposures at
25 relevant human occupational and environmental exposure levels. It is only with such
26 justification that EPA should consider including such derived uncertainty factors before
27 its draft Cumulative Risk Assessment Framework (May 2002) is finalized.

28

1 7. CHARGE QUESTION 5

2
3 7.1. Agency Charge Question and Suggested Areas for Inquiry

4
5 Charge Question: Does the assessment adequately discuss the derivation of a
6 range of estimates for the cancer risk? Are there any studies that should/should not have
7 been included?

8
9 Suggested Areas for Inquiry: There is some question about whether the draft
10 assessment should condense the range into a single "point" estimate. Does the draft
11 assessment adequately present the case for a range of estimates? A key question for each
12 tumor site is the choice of a linear or a nonlinear approach based on the mode(s) of action
13 at that site. Does the draft assessment adequately describe how the available data on
14 mode of action would support either a linear or a nonlinear approach?

15
16 7.2. Panel Response

17
18 7.2.1. The Range of Risk Estimates

19
20 The Panel commends EPA for the derivation of a set of cancer risk estimates or
21 cancer slope factors (CSF) for TCE in the draft assessment. The presentation of a range
22 of estimates is a step forward for EPA towards a more explicit and more quantitative
23 representation of the substantial uncertainties in estimates of cancer risks.

24
25 The Panel does not recommend reducing the range of CSFs into a single "point"
26 estimate, either a geometric mean or another measure of central tendency. Reasons for
27 not reducing the range of the CSFs into a single number have been given in the draft
28 assessment sufficiently clearly and exhaustively.

29
30 On the surface, the estimation and the rationale underlying the presentation of a
31 range of cancer estimates appear to be reasonable and informative. Further investigation
32 of this new approach for risk assessment is, however, warranted

33
34 The Panel recommends that the Agency improve its presentation of the cancer
35 slope factors and discussion of the scientific rationale for choices made. Several
36 suggestions for improvement appear below.

37
38 7.2.1.1 Clarification of the Cancer Slope Factors

39
40 The Panel discussed suggestions for clarification. They directly concern
41 improving the derivation of the risk estimates using the data available for TCE.

42
43 a) One obvious addition to the present content of the draft assessment should be a
44 detailed presentation of how each study contributed to the set of cancer slope factors. All
45 available information should be provided to enable other risk assessors to reproduce the
46 derivation of the individual cancer slope factors used in the risk assessment procedure for

1 TCE. The reason of choosing a study should be explained and the type and wealth of data
2 used for the cancer slope factors calculation should be described. The derivation of exposure
3 estimates should be given and their strength and weaknesses should be discussed on a
4 study by study basis. More detail on the exact calculations used would be helpful in a
5 technical appendix. With such a presentation, the Agency will elaborate as transparently
6 and as explicitly as possible the approach it has used for the derivation of each of the
7 cancer slope factors in the draft assessment.

8
9 This presentation should include several specific revisions of the:

- 10
11 1) Introductory statement "Several cancer slope factors were developed,
12 with most between 2×10^{-2} and 4×10^{-4} mg/kg-d."
13
14 2) Definition of the slope factor (pages I -7 and 4-15)
15
16 3) Explanation of the overall approach of deriving this set of alternative
17 estimates (e.g., pages 4-1, 4-2).
18

19 EPA's own responses provided to the Panel in its "Summary of Public Comments
20 for EPA's Science Advisory Board" with regard to question 5 already contains valuable
21 information to be used in such a presentation.
22

23 b) It appears that calculations of exposures for the Finnish cohort (Anttila, et al.,
24 1995) were based only on the urinary TCA measurements for the cancer cases (see page
25 4-16, line 13pp). If this is what was done, the exposure estimates should be revised to
26 include the full group(s) of workers who were at risk - not just those who ultimately
27 developed the cancers. Also, for the occupational epidemiological study-based
28 calculations as a whole, it is not clear that there was a correction for the healthy worker
29 effect (or the healthy worker survivor effect, whereby healthier lower-background-risk
30 people tend to stay on jobs longer and receive greater exposures) (***) see page 4-16, line
31 26pp).
32

33 c) Public comments raised on the correct use of the clonal two-stage
34 carcinogenesis model (Moolgavkar-Venzon-Kundsen two-stage model of carcinogenesis)
35 for biologically based mechanistic modeling should be considered very carefully. The
36 Panel advises the Agency to carefully document the description of the modeling itself and
37 especially the underlying data so that other risk assessors can replicate those evaluations.
38 Therefore, the data of the Finnish study should be obtained again so that others may
39 repeat the biologically based mechanistic modeling work. The Panel encourages research
40 to improve biologically based mechanistic carcinogenesis modeling for TCE.
41

42 d) Special problems that could arise in the use of ecological studies (New Jersey
43 Drinking Water Study (Cohn et al., 1994)). Whether there are such ecological studies
44 should be discussed in the draft assessment (section 4.5.1.3).
45

1 e) The Panel finds that footnotes in Chapter 1 are very helpful for readers. More
2 footnotes in other sections in the present Chapter would further help understanding the
3 discussion better. For instance, there is a need to explain:

- 4
- 5 1. p. 4-16, line 16, the number of 2.956. Where did it come from?
- 6
- 7 2. p. 4-18, line 28, genotype GSTM/GSTT
- 8
- 9 3. Table 4-1, the ratio of 97.5 percentile/2.5 percentile equals
10 the span of the 95% confidence interval. What is meant exactly by this?
- 11

12 These are only some examples.

13

14 7.2.1.2 Suitability and Use of the Cancer Slope Factors

15
16 Several further issues need to be addressed, clarified or discussed for making the
17 current derivation of the range of cancer slope factors better suitable for the risk
18 assessment of TCE.

19
20 a) The meaning of the “upper bound” figures quoted needs to be clarified (e.g.
21 page 14-19, line 27-28) Are these 95% confidence upper bounds considering only the
22 statistical sampling error? What additional uncertainty would be expected from the
23 uncertainty in the estimates of long term exposures? Can upper bounds on the cancer
24 slope factors be defined for human exposure?

25
26 b) Estimates of cancer risks for different target organs should not be seen as
27 alternatives to one another; but such risks should add for the typical person who has a full
28 complement of a liver, kidneys, and other potentially at-risk organs. Competing causes of
29 cancer mortality or complementary risks from different cancer sites should be taken into
30 consideration when presenting site-specific cancer slope factors.

31
32 c) Adequacy of the PBPK dose estimates for use to derive CSF should be
33 discussed in each case. It should be investigated how far uncertainties identified during
34 PBPK-modeling induce uncertainties on the cancer slope factors. The draft assessment
35 should explain in more detail the differences between the Fisher et al.-model and the
36 Clewell et al. PBPK models. (See also the Panel response to Charge Question 6.) The
37 discussion of those differences can then be related to Bois's uncertainty analysis results.

38
39 d) Show how the conversion of TCA and DCA area under the curve metric
40 between the chronic oral route and chronic inhalation route of exposure can be / has been
41 performed (Section 4.2.3 of the draft assessment). Has there been a model applied?
42 Which assumptions are used?

43
44 e) The set of cancer slope factors describing the range may be characterized by different
45 uncertainties (sampling errors in the case of cancer slope factors derived from animal
46 experiments, more complicated variability in the case of cancer slope factors derived

1 from human studies) that should be addressed when presenting the range. Such
2 characterizations are appropriate to help understand the role of the range of the cancer
3 slope factors and prevent this range being naively interpreted as a range of high
4 probability of the location of a true cancer slope factor.

5
6 f) The reader is not provided with an integrated treatment of comparable
7 uncertainties for the different data inputs and routes to calculation. For the animal-based
8 estimates, it appears that linear projections have been made from LED10's. Was some
9 upper confidence limit calculated in the derivation of cancer potency factors from the
10 human studies? Why should the statistical uncertainties built into the LED10's be treated
11 differently from the uncertainty resulting from the use of different data sets, different
12 estimates of exposure for the human studies, different pharmacokinetic models, or even
13 different assumptions about the relevant dosimeter for particular endpoints? Sections
14 4.5.3-4.5.5 should be revised by taking those considerations and questions into account.

15
16 g) There is no weighting of the different bases for estimating TCE cancer risks.
17 (Do we mean here the different bases of animals vs. humans and or the different bases
18 provided as tumor site location?) Implicitly all values within the selected range are
19 treated as equally likely, and there is no representation of the likelihood that the true
20 population risk could lie outside the summary range provided.

21 22 7.2.1.3 Improved Mediation of the Cancer Slope Factors

23
24 For a better understanding of the role of the range of cancer slope factors for
25 assessment of TCE risks and for using the range for guidance in deriving exposure limits
26 in specific risk management problems, the strengths and limitations of this new approach
27 should be discussed in the draft assessment. This discussion should address the following
28 points:

29
30 a) The range is not an interval estimate in the sense of a statistical confidence
31 interval and its concept is not grounded in a sampling model for populations. This
32 reasoning provides actually another argument for not calculating a central tendency value
33 (see also above, section 7.2.1.2 g).

34
35 b) The stability and robustness of the range as it is derived at present should be
36 discussed in light of the perspective that a new study may appear exhibiting estimates at
37 the lower or at the higher end of the current range. The sources of disturbance against
38 which robustness is lacking should be explained in more detail, e.g., referring to the
39 factors reflecting human variation, sensitive populations, and susceptibility, as described,
40 specified in sections 1.6 and 3.3 of the draft assessment.

41 42 7.2.2. Further Studies to Be Included

43
44 The question posed to the panel about the inclusion or exclusion of specific
45 studies raised three issues.

1 a) The study of Hansen et al. (2001) should be included for the risk assessment of
2 TCE and in particular for the derivation of cancer slope factors specific for the dose-
3 response data available for this study. New valuable information for TCE cancer risk is
4 expected for non-Hodgkin lymphomas, esophagus cancer and cervix cancer. The
5 adequacy of a German study of Tesch et al for inclusion was also raised and the agency
6 should check for this.

7
8 b) Where epidemiological studies are the basis of risk estimates, EPA should
9 review and consider all studies (positive and negative), and then make a separate
10 determination about which studies to use to calculate the cancer slope factor. These
11 studies should be the ones, among the studies that are well designed, that would generate
12 the most health-protective number. To select only studies with "statistically significant"
13 results risks introducing a bias that good meta-analysis practice would avoid.

14
15 c) Exposures in most of the epidemiologic studies could be estimated. For
16 example, the Hill Air Force Base study did not report exposures in ppm, but there are
17 monitoring data that would provide as accurate a guideline as using toxicologic data with
18 a 10-20-fold adjustment.

19 20 7.2.3. Linear or Nonlinear Approach

21
22 The choice of a linear or a nonlinear approach for each tumor site is based on the
23 mode(s) of action at that site. The Agency has clearly explained in the draft assessment
24 the criteria for the choice of the linear or the non-linear approach separately by tumor
25 site. It has also described the key limitation of the nonlinear analyses, which are the
26 uncertain identity of the active metabolites and the key events involved in TCE-induced
27 cancers in humans and in animals. Whereas the linear approach represents a best estimate
28 for the case where one believes the mode of action is direct or indirect interaction with
29 DNA and human interindividual variability is not very large (see Hattis and Barlow,
30 1996), the nonlinear approach is used to quantify the extent of uncertainty and to
31 incorporate this into the determination of RfD and RfC estimates.

32
33 The draft assessment does describe in Section 3.5 how the available data on mode
34 of action would support either a linear or a nonlinear approach. However, the critical
35 modes of action for choosing the nonlinear extrapolation should be explained in more
36 detail. The EPA needs to provide the quantitative type of analysis of MOA supporting
37 non-linear modes of action that was included in some of the state of the science papers
38 (e.g. Bull, 2000)

39
40 The compilation of the cancer estimates in Figure 4-3 provides an excellent
41 overview on the linear and non-linear results as far as they were obtained from available
42 data. The Panel also notes that non-linear projections were made from LED10s for liver
43 and testis

44
45 There was disagreement on whether non-linear extrapolation on the basis of
46 mechanistic modeling leads to reliable risk estimates. Problems with the application of

1 biologically based models are demonstrated in the draft assessment. Ambiguities in the
2 determination of the uncertainty factors in the non-linear extrapolation complicate a
3 straightforward comparison of risk estimates obtained by both methods (the linear and the
4 non-linear) for one tumor site.

5 6 7.2.4. Sensitive Populations

7
8 The Panel commends the agency for providing the sections on sensitive
9 populations and cumulative risks (pages 4-29, 4-30). It notes, however, that the draft
10 assessment incorrectly suggests that the different slope factors apply to different exposed
11 population characteristics (page 4-30, lines 1-6) and that the various cancer slope factors
12 are not based on variability in human sensitivity.

13 14 7.2.5. For Further Consideration

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

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

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

1 8. CHARGE QUESTION 6

2
3 8.1. Agency Charge Question and Suggested Areas for Inquiry

4
5 Charge Question: Please comment on the use of calibrated models and uncertainty
6 analysis to address the question of pharmacokinetic model uncertainty.

7
8 Suggested Areas for Inquiry: The calibrated models (Bois, EHP 2000a, 2000b)
9 build on the pharmacokinetic models (Fisher, EHP 2000; Clewell et al, EHP 2000) by
10 fitting them to additional datasets. Is the draft assessment's use of the calibrated models
11 adequately discussed and supported? In addition, Bois's uncertainty analyses indicate the
12 extent of uncertainty in the dose estimates calculated for the liver, lung, and kidney. Is
13 the draft assessment's use of these uncertainty analyses to characterize pharmacokinetic
14 uncertainty adequately discussed and supported?

15
16 8.2. Panel Response

17
18 The Agency is commended for including PBPK modeling and its uncertainty
19 analysis into the risk assessment of TCE. By this the Agency steps forward to meet with
20 recent demands to emphasize applicable methods for characterizing uncertainty in risk
21 assessment which has reached a state of applicability. The Panel encourages EPA to
22 proceed further in this direction and to include PBPK modeling into the risk assessment
23 process with identification of the uncertainty in model structure and parameters.

24
25 Therefore, an uncertainty analysis should remain in the draft assessment and
26 should be used for derivation of different dose metrics. The Panel advises the Agency to
27 show that uncertainty has been assessed on the best available scientific knowledge of the
28 toxicokinetics and toxicodynamics of TCE. The use of an uncertainty analysis for the
29 derivation of different dose metrics is useful for a more realistic dosimetry (the
30 toxicokinetic part) for the dose-response assessment. The Agency might, however, also
31 explore formally including the toxicodynamic elements into a more comprehensive
32 uncertainty analysis (uncertainty of causal effect models).

33
34 The issue of uncertainty between the two models of Fisher et al. (2000) and
35 Clewell et al. (2000) is a natural evolution of a relatively new area. In this case, Dr.
36 Bois's application of statistical methods (2000) to reduce the level of uncertainty helped
37 to strengthen the argument for application of PBPK modeling in this risk assessment
38 process. Presently, there are at least 700 papers on PBPK modeling and the area is more
39 than mature enough to be utilized by the Agency to meet its commitment in its cancer
40 risk assessment guidelines to use biologically based modeling (USEPA 1999). In many
41 ways, this risk assessment of TCE serves as a role model for the next generation of risk
42 assessment draft assessments from EPA.

43
44 The state-of-the-science papers on the uncertainty of PBPK models (Bois, 2000a
45 and 200b, have been useful to aid in how to credibly apply the results of the Fisher and
46 Clewell's pharmacokinetic models. Obviously, PBPK modeling should be accompanied

1 by a realistic uncertainty analysis. However, one has to be aware that in the present case
2 this is a multi-step approach based on assumptions and further uncertainties. The risk
3 estimates and uncertainties reported in the draft assessment result after a three-step
4 procedure extracted from the SOS papers in the EHP Supplement Volume of 2000,
5 namely:

- 6
- 7 a) the basic but different Fisher and Clewell models
- 8
- 9 b) the Bois uncertainty analysis
- 10
- 11 c) the use of the Bois results in the Rhomberg paper (2000).
- 12

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

17
18 Specific issues related to modeling and uncertainty analysis that the Panel thinks
19 are necessary for the clarification and the improvement of the Agency's draft assessment
20 are explained below.

21 22 8.2.1. Modeling

23
24 Using pharmacokinetic models that estimate the target tissue dose for the key
25 metabolites identified in the toxicity and carcinogenicity of TCE is an extremely useful
26 tool. The Agency has recognized this by using these models in the draft assessment of
27 TCE. Although these models in the assessment have their limitations in describing the
28 complex toxicokinetic reality, they are now evolving, perhaps to a point at which they
29 can be used to identify) experimental data to further verify the ability of the current
30 models to predict levels of TCE and metabolites in the various target tissues.

31
32 As described in the draft assessment there are two PBPK models for TCE: one
33 published by Fisher (2000) (F) and one by Clewell et al., (2000). The basic structural
34 differences between these models are briefly reviewed in this assessment draft
35 assessment (4.2.1) but not the differences in estimation of key parameter values. A
36 critical evaluation of both these models needs to be included in this section prior to a
37 discussion of the recalibration of these models by Bois (2000a,b). This discussion is
38 necessary to understand each individual model as well as the parameter uncertainty
39 associated with that model. . The new discussion should explain the basic features of
40 model building, prior information, new data and posterior information of the calibrating
41 models of Bois. It is also necessary to outline the differences between the simulations
42 performed by Clewell and the Bayesian hierarchical modeling of Bois. The discussion
43 should also seek to identify and describe the reasons why the Fisher and Clewell models
44 seem to make divergent dosimetric predictions, and the likely sources of the residual
45 differences between the model predictions after the Bois recalibration. . The draft
46 assessment mentions on page 4-3 that a Bayesian statistical framework and Markov-

1 Chain Monte-Carlo (MCMC) simulation was used to refine the Fisher and Clewell model
2 by Bois (2000) using more data sets to estimate each model's parameters. It is also stated
3 that the result is a set of calibrated models that better fits a wider range of experimental
4 data. This discussion raised several issues in the Panel.

5
6 a) Bois used the Clewell model with three modifications: 1) one compartment was
7 added to describe the closed chamber exposures to mice to describe Fisher's gas uptake
8 data; 2) the volume of the poorly perfused compartment was changed, but it was not clear
9 in Bois's paper what this value was changed from, what it was changed to
10 and why; and 3) how the computation of the blood flow to the richly perfused
11 compartment was revised. It would be useful for the Agency to include in this section a
12 discussion of what were the specific data sets that were used by Bois to update these
13 models and how these specific data help in parameter estimation. In reviewing Bois's
14 model (2000b) it appears that gas uptake data may have been the only new data set used
15 for model calibration and estimation of variability and uncertainty. The Agency needs to
16 include in the assessment a discussion concerning the limitations of only using gas uptake
17 data for this purpose since it is an indirect measure of metabolism.

18
19 b) The characterization of the uncertainty and the use of PBPK models and their
20 uncertainty analysis models should be fully described in the draft without requiring
21 extensive consultation of the state-of-the-science papers in the EHP supplement issue
22 (e.g., through an electronic appendix, including data and programs if available). Full
23 documentation of the original data is recommended. The Panel also thought it important
24 to identify which data were selected for the assessment and which were not and the
25 rationale for the choices that were made in this respect.

26
27 c) Bois's modeling is a comprehensive modeling of all aspects of the
28 pharmacokinetic modeling of derived dose metrics. Reproducibility of the methods used
29 by Bois is a question of concern. All assumptions going into the model should be made
30 clear. The Panel asks if the models be made publicly available? Additional analyses are
31 required that the results of Bois are correct. If the risk assessment of TCE is based on the
32 state-of-the science papers, it is necessary for the model to be available for independent
33 use to reproduce of the analyses and to check it.

34 35 8.2.2. Uncertainty Analysis

36
37 Parameter uncertainty arises from many sources such as measurement errors or
38 the use of surrogate data (indirect measurements of parameter values) such as in the case
39 of gas uptake data where changes in parent compound in a closed chamber are measured
40 instead of observations of concentrations or generation rates of specific metabolites.
41 Concern for parameter uncertainty should be discussed in this section of the assessment.

42
43 Model uncertainty arises due to gaps in understanding the specific mechanism(s)
44 that affect both the kinetics and the dynamic actions of the compound in question. In
45 section 4.5.7.1, the draft assessment states that the full extent of model uncertainty cannot
46 be quantified, only the models that have been analyzed This is an appropriate warning to

1 the reader that the extent of model uncertainty that can be quantitatively assessed is
2 limited by the analysts' creativity and the resources available for examination of
3 alternative conceivable model structures consistent with available biological
4 understanding. There appears to be model uncertainty with respect to the Fisher and
5 Clewell models. The performances of different models with the same data sets can be
6 compared on the basis of a common measure of goodness of fit. It is not made clear how
7 the Bayesian method contributes to the analysis and how they use all the available
8 information to judge the relative likelihoods that different models are right.

9
10 Several areas for improvement were identified. First, the type of uncertainty
11 covered by the pharmacokinetic models of Bois on the basis of the Fisher and the Clewell
12 models should be explained in much more detail within the draft assessment, in a way
13 that enables the reader to assess the benefits and the limitations of these analyses (e.g.,
14 further explanation in terms of lack of knowledge and variation between individuals).
15 The impact on the dose estimates of the Fisher and Clewell models and the Bois
16 modeling should be exhibited to a larger extent and discussed critically before using the
17 Bois results to define the uncertainty and variability in the dose metric used for the
18 derivation of cancer slope factors and the consequent uncertainty and variability in the
19 cancer slope factors themselves. Another part of the model uncertainty that can be
20 quantified is the differences in expected risks that are produced by assuming that one
21 dose metric is the correct predictor of the risk of cancer at a particular site, relative to the
22 risk produced by selecting another dosimeter.

23
24 Another part of the model uncertainty that can be quantified is the differences in
25 expected risks that are produced by assuming that one dose metric is the correct predictor
26 of the risk of cancer at a particular site, relative to the risk produced by selecting another
27 dosimeter. In particular, the impact of the uncertainty analyses on dose responses in
28 humans should be addressed. Sources of the differences between the Fisher and Clewell
29 models and their implications on the central estimates and on the output of the models
30 and how they translate in dose and risk estimates should be provided. It is important see
31 how values are fed from one model into another. Median results taken only as dose
32 estimates are not enough. It is necessary to use other percentiles of the distribution (or
33 preferably a representative sampling of different outputs from the distributions of each
34 plausible dosimeter) and define the effects on the distribution of risks.

35
36 The second area for improvement involves sources of uncertainty revealed by this
37 modeling approach. These sources, assumptions about the parameter values and their
38 variation, transfer of a number of parameter estimates between species, should be
39 discussed and related to the gain in precision obtainable through this calibration.
40 Skepticism about the posterior distribution, the comparability of the prior and the
41 posterior parameters and the sensitivity of the Bois model should be addressed by
42 reviewing the weights that the Bois model places on the new calibrating information
43 relative to the prior distributions. Prior information may not be being given the weight it
44 deserves or new calibrating information may be evaluated as having less uncertainty than
45 it should.

46

1 The Panel noted several concerns related to the characterization of uncertainty.

2

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

12

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

18

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

22

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

27

28

29 8.2.3. Data Availability

30

31 Questions have been raised on the cleanness or completeness of the data used in
32 this modeling (e.g., DCA values reported to contain errors). It was also noted that Bois
33 was given an early version of the new Fisher model that was changed by the time the
34 mice and human model reached publication and that there are new mouse and human data
35 from Fisher available. This should be checked and if there are errors or unexplainable
36 inconsistency, a re-analysis should be performed on order to get appropriately revised
37 dose estimates, even if those errors were of minor influence on the final risk estimate.
38 Therefore it is strongly recommended to disclose the sources of the data which were used
39 for this TCE risk assessment and to describe their availability. The full power of the Bois
40 modeling is obtained only if all available data are used.

41

42 8.2.4. Markov-Chain Monte Carlo (MCMC)

43

44 The section where the statistical analyses of the pharmacokinetic models are
45 described (Section 4.2.1, 3rd paragraph) should be completely rewritten to describe very
46 clearly and precisely the methods applied by Bois. Since this method has been discussed

1 widely, the Panel advises the Agency to provide (e.g., in an appendix) a comprehensive
2 summary of this methodology with a few key references. Without going too much into
3 the details, the basic concept of the Bayesian hierarchical modeling should be outlined
4 and the role of the MCMC method within the use of the Bayesian hierarchical modeling
5 clarified, namely for the calculation of posterior distributions and the numerical
6 integration necessary to achieve this calculation.

7
8 8.2.5. For Further Consideration

9
10 Finally, the Panel likes to add a remark made by one member on dynamic
11 modeling which goes beyond the present question but is thought to be important for the
12 refinement of the risk assessment of TCE in particular.

13
14 In presenting the results of clonal growth modeling the Agency is again
15 commended for pushing the envelope by including this approach in this risk assessment.
16 This presentation involves more extensive data than those used in many previous PBPK
17 modeling studies.

18
19 The Panel advises the Agency to correct the problem of poor draft documentation
20 and record keeping in its use of modeling by getting the Anttila data and recreating the
21 model and data reported by Dr. Chao Chen in the State-of-the-Science paper. This is very
22 important for allowing others to review its work and conduct their own modeling in line
23 with the Agency's policy of openness and transparency.

1 9. CHARGE QUESTION 7

2
3 9.1. Agency Charge Question and Suggested Areas for Inquiry

4
5 Charge Question: Is it appropriate to consider background exposures and other
6 characteristics of an exposed population as modulating the risk of TCE exposure in that
7 population?

8
9 Suggested Areas for Inquiry: The draft assessment discusses the case that TCE's
10 toxicity can be modulated by background exposures to TCE's metabolites. A modifying
11 factor is proposed because the data for estimating the effect of co-exposures may not be
12 available to risk assessors in the field, but the potential for modification of TCE's toxicity
13 is present. How can the potential effects of co-exposure be best addressed?

14
15 9.2. Panel Response

16
17 The Panel was pleased that the Agency has taken the first steps of including the
18 issue of cumulative risk in a health risk assessment. Although there was agreement that
19 background exposures to TCE and/or metabolites is a very important issue, there was
20 disagreement, as noted in section 6.2.3 of this report, about whether the RfD should be
21 the method by which this background exposure is addressed.

22
23 In light of the prevalence of some ubiquitous background exposures in the general
24 population, some panel members thought it prudent to apply a modifying factor to the
25 RfD. This factor would address exposures shared by all and not simply due to site-
26 specific scenarios best addressed by risk managers.

27
28 Other panel members argued against including an uncertainty factor for
29 background exposure, because EPA is in the process of finalizing the cumulative risk
30 assessment approach that provides a framework for taking background exposure into
31 account separately from the derivation of the RfD. Since RfDs are often compared for
32 priority setting, it is essential that a consistent approach to handling background be taken.
33 In addition, total background exposures may best taken into account through a thorough
34 aggregate/cumulative exposure assessment for a specific scenario that needs to be
35 addressed.

36
37 Another view noted that, unlike the RfD, the RfC was largely derived from
38 human studies, and thus already incorporated these background exposures (because the
39 study subjects likely had similar background exposures as the general population).
40 Therefore, it was a reasonable argument for not applying the modifying factor.

41
42 If EPA decides to include an uncertainty factor for background, it will be essential
43 for EPA to include a rigorous discussion of the evidence that a cumulative effect is
44 expected at human exposure levels based on the modes of actions proposed. Some
45 members of the panel proposed that EPA utilize the available quantitative data and model
46 the cumulative effect based on general background for human exposure levels.

1
2 The Panel agreed that regardless of EPA's final policy decision on whether or not
3 to include an additional uncertainty factor in the RfD for background exposure, the
4 Agency should detail more completely its reasons for choosing, or not choosing, such an
5 uncertainty factor. Specific comments related to this issue follow.

6
7 Humans are never exposed to only one agent in isolation. Particularly insofar as
8 multiple exposures may share modes of action, common metabolic pathways, et cetera, it
9 seems appropriate to consider background exposures of an exposed population as
10 modulating the risk of TCE exposure. It is highly appropriate for EPA to consider
11 background exposures to TCE's metabolites and to other compounds that produce the
12 same metabolites, because the range of estimated adult doses for the general population
13 for some of these compounds are comparable to or even exceed the range of estimated
14 doses for TCE (Table 2-1 of the TCE Draft Risk Assessment). For example,
15 tetrachloroethylene, which is metabolized to TCE, is present in the ambient air at levels
16 10 times higher than TCE. The same is true for the presence in water of the chlorination
17 byproducts, DCA and TCA, both of which are metabolites of TCE. DCA and TCA may
18 be the active metabolites for some of the TCE's adverse effects, such as hepatomegaly
19 and hepatic carcinogenesis. Thus, background exposures to these compounds clearly
20 have relevance to the risk of exposure to TCE.

21
22 Understanding and measuring these background exposures presents many
23 methodological issues. The human studies that state TCE is a primary exposure are still
24 dealing with mixtures. For example, TCE was a primary exposure at Hill AFB but
25 subjects were generally exposed to jet fuels such as JP- 4 (now JP-8) on a daily basis as
26 well as other solvents besides TCE (LeMasters et al. 1997,1998; Stewart 1991). The
27 Wilson et al. (1998), cardiac malformation study is a prime example of the challenge that
28 this draft assessment faces with human studies having TCE as the primary exposure. In
29 section 3.4.5.1 of the draft assessment, it was reported that "women exposed to
30 degreasing solvents, including TCE have reported elevated risks for cardiac anomalies in
31 their offspring ... with an attributable risk of 4.6%" for hypoplastic left heart anomalies.
32 The investigators, however, only asked the parents regarding their exposure to
33 "solvents/degreasing compounds" but no specific mention of TCE was in the entire
34 study. Further, it was not clear whether or not the mother or father was exposed, but
35 what was known is that for 98% of the cases the mother was interviewed and in 20% of
36 the cases the father was present. In fact, generally it is unlikely the individuals know the
37 exact compounds contained in degreasing or solvent exposure. This has been a common
38 experience from interviewing numerous men and women at sites such as Air Forces
39 Bases (see Hill AFB and articles by LeMasters et al. 1997, 1999). This suggests that
40 based on the human studies, we cannot specifically implicate TCE, but can only use these
41 studies as supportive evidence. The Agency needs to develop a rigorous way of
42 interpreting these studies and incorporating them into its assessment of background
43 exposures.

44
45 In light of the prevalence of such exposures in the general population, some Panel
46 members thought it prudent to apply a modifying factor to the RfD, as is argued in

1 Section 4.3.3 of the draft analysis. These panel members felt that in cases where data are
2 available for estimating these co-exposures for all relevant populations, the modifying
3 factor could be omitted. Some other panel members thought it reasonable not to apply the
4 modifying factor to the RfC, and agreed with the Agency's argument that, unlike the RfD,
5 the RfC was largely derived from human studies, and thus already incorporated these
6 background exposures (because the study subjects likely had similar background
7 exposures as the general population). Yet another view was that the application of a
8 modifying factor for background exposures was not appropriate.

9
10 The Panel felt that Tables 2-1 should include data on the estimated TCE
11 metabolite levels derived from the TCE-related compounds. In particular there is the
12 need to estimate quantitatively how these background exposures would affect the risk of
13 TCE. This should be used in a justification of a 3-fold factor (or some other factor)
14 applied to the RfD for background and co-exposures.

15
16 Besides background levels of TCE, its metabolites, there are lifestyle exposures
17 and other co-exposures that will theoretically modulate TCE metabolism, utilize the same
18 metabolic pathways, or share targets of toxicity with TCE. Examples are acetaminophen
19 and ethanol, which can theoretically alter susceptibility to TCE effects by influencing
20 CYP2E1 activity. This leads to the recommendation that a table be developed which
21 provides a list of relevant exposures that modulate CYP2E1 with information that can be
22 used to estimate the impact on TCE risk. In particular how these exposures can be used
23 to justify the choice of the 3-fold factor applied to the RfD. Concerns were expressed for
24 diseased individuals (diabetes, hepatitis, HIV positive, etc.), who may be especially
25 susceptible to TCE exposure. It is not clear whether their increased risk will fall within
26 the 10-fold RfC population variability factor. Some further discussions on these potential
27 high-risk individuals would be helpful.

28
29 Finally, the Panel felt that this important area of cumulative risk required more
30 detailed treatment as it especially relates to TCE.

31

1 10. CHARGE QUESTION 8

2
3 10.1. Agency Charge Question and Suggested Areas for Inquiry

4
5 Charge Question: Do the data support identifying risk factors that may be
6 associated with increased risks from TCE exposure? Are there any risk factors that
7 should/should not have been included?

8
9 Suggested Areas for Inquiry: Does the draft assessment adequately present and
10 consider the data supporting identification of potentially susceptible populations,
11 including the role of differences in enzyme activity to affect TCE's metabolism and
12 toxicity?

13
14 10.2. Panel Response

15
16 Yes, the data support identifying numerous risk factors that may be associated
17 with increased risks to susceptible subpopulations from TCE exposure. The EPA draft
18 assessment has done a good job identifying the general areas of concern related to
19 prenatal, reproductive and developmental risks associated with TCE exposure, especially
20 given the level of information known to date.

21
22 A major issue is related to multiple exposures and routes of exposure to
23 susceptible groups from background exposures to ethanol, TCE and its metabolites,
24 chemical solvent mixtures and the limited data available for perhaps the most susceptible
25 population, the embryo/fetus, infant, and child given the data found in Table 2-1. The
26 Panel notes that that none of these exposures are voluntary to the fetus, newborn and
27 infant. The implication of levels of exposure found in the ambient environment and
28 relevance of exposure that might be found in breast milk, the fetal compartment or in
29 other areas where infants are exposed such as with preparation of formula with TCE
30 contaminated water supplies are basic areas of extrapolation. This approach could then
31 serve as a long-term guide for future agents toward evaluating reproductive, prenatal, and
32 childhood environmental exposures related to age specific effects. Numerous other
33 potentially susceptible populations were identified and discussed, including individuals
34 with underlying diseases that alter their metabolism of TCE, individuals on medications
35 that alter CYP2E1, and individuals with diseases that put them at higher risk for
36 developing kidney cancer, liver cancer, lymphoma, and other diseases.

37

1 11. CHARGE QUESTION 9

2
3 11.1. Agency Charge Question and Suggested Areas for Inquiry

4
5 Charge Question: Do the data support the possibility that TCE can affect children
6 and adults differently? How can this be reflected in the quantitative assessment?

7
8 Suggested Areas for Inquiry: Given the potential for differences between children
9 and adults, does the draft assessment develop toxicity values that are protective of
10 children, including minimization of exposure through human milk? Does the draft
11 assessment adequately consider the information on differences in metabolism and
12 clearance between children and adults and appropriately characterize the potential for
13 differences in response? With the data at hand, are there ways to make the
14 characterization more quantitative? Does the TCE database warrant an explicit
15 uncertainty factor to reflect data gaps concerning the potential risks to children?

16
17 11.2. Panel Response

18
19 11.2.1. Major Summary Consensus Points of the Panel

20
21 The Panel reached consensus on the following conclusions related to this charge
22 question:

23
24 a) The data presented supports the possibility that TCE can affect children
25 differently than adults, although there is a very limited database of TCE in children due to
26 lack of directly applicable studies. Based on the TCE database, children appear to be at
27 greater risks than adults from TCE exposure, due to possible differences in exposure,
28 metabolism, and clearance. In regard to end organ susceptibility, data from other solvents
29 and neurotoxicants, in general, would indicate that the child's central nervous system
30 function is potentially more susceptible to TCE than the adult.

31
32 b) The draft does not explicitly discuss whether or not the uncertainty factors
33 address risk to children or attempt to develop toxicity values that take children into
34 consideration.

35
36 c) The Panel advises the Agency to provide a more complete discussion of the key
37 articles and information relevant to the issue of differences between children and adults.
38 The Panel recommends that there be a stand-alone comprehensive children's chapter that
39 discusses all the children's issues, including exposure, susceptibility during pregnancy,
40 pharmacokinetics, and pharmacodynamics, in addition to discussions of developmental
41 animal and children data in every section.

42
43 The Panel advises the Agency to include in that chapter a discussion of the need
44 for, or lack of need for, an additional quantitative children's uncertainty factor.
45

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

8
9 In regard to the issue of an additional uncertainty factor for children, several
10 members of the Panel felt that the data supporting the possibility that TCE can affect
11 children differently than adults led to the conclusion that it would be prudent for EPA to
12 add an additional uncertainty factor to protect children. They believed this additional
13 factor was merited, based on heightened concern for children, given existing information,
14 and also based on the uncertainty of the TCE risk assessment, given the limited
15 developmental toxicity data available.

16
17 Others agreed that children are at possibly greater risk, but felt that the existing
18 composite uncertainty factor of 3,000 for the RfD was already large and adequately
19 protective of children. They suggested that a component of the "other uncertainty factor"
20 (see section 6.2.3. of this report) established to cover a wide range of uncertainties
21 involving susceptibility and background could be explicitly identified as a children's
22 uncertainty factor. Yet another view was that the 50-fold human variability uncertainty
23 factor for the RfD in the draft assessment was probably large enough that an additional
24 factor for children was unnecessary. However, an additional uncertainty factor for
25 children may be warranted for the RfC, which currently only includes a 10-fold factor for
26 human variability.

27
28 This discussion emphasizes the importance of the inter-relationships among
29 various components of the Agency's risk assessment (again see section 6.2.3. of this
30 report). It also underlines the importance of the Panel's advice that the Agency explicitly
31 address the need for, or lack of need for, an additional quantitative uncertainty factor for
32 children and clarify how that factor relates to other uncertainty factors used.

33
34 In regard to cancer and children's susceptibility, the Panel notes another issue
35 concerning the complexity of the TCE assessment. The Panel notes how the issue of
36 children's susceptibility is closely linked to the Agency's overall risk assessment
37 approach. In response to Charge Questions 5 and 8, the Panel raised concerns about
38 childhood leukemias and lymphomas associated with drinking water contamination (New
39 Jersey Drinking Water Study). It should be noted that this is the only data set used by
40 EPA to address children's cancer risk differently from adults. Thus, if EPA were to
41 decide to not include that study in its determination of cancer risk, then an adjustment of
42 the cancer slope factor would be needed to address the children's cancer risk issue

43 44 11.2.2. Background to the Panel's Conclusions

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

7
8 Generally accepted knowledge of the pharmacokinetics and pharmacodynamics of
9 TCE, its metabolites, solvents in general, and many xenobiotics support the overall
10 conclusion that children, as compared to adults, are potentially at greater risks from TCE
11 and its metabolites. If one takes an approach based on pharmacokinetics and
12 pharmacodynamics, the embryo, fetus, infant, child and adolescent (referred from here
13 forward only as the "child"), as compared to the adult, have altered TCE exposure,
14 absorption, metabolism, clearance, and potentially end organ susceptibility.

15
16 In regard to absorption, the Panel notes that the human is exposed to TCE and its
17 metabolites transplacentally, transmammillarily, and through the same routes as the
18 adult. In one animal study, TCE appears to accumulate in the fetus and amniotic fluid
19 during development. This would indicate that compared to mother, the developing human
20 might have greater exposure. In addition, the child drinks more water and breathes more
21 air than the adult, so exposure would be greater. Considering the large number of
22 drinking supplies that have TCE, these exposure-related factors are of great concern.
23 While there was agreement that differences in exposure assessment should be discussed
24 more rigorously, including data that quantifies these differences, there was no agreement
25 on whether this difference in exposure should be the basis for additional uncertainty
26 factors. Further, there is no reason to believe that the absorption of the developing
27 human should transdermally should be less than adult absorption. In fact, since the infant
28 has greater skin surface area by a factor of 2-3 on a per kilogram basis, they should
29 absorb more TCE from the transcutaneous route than the adult.

30
31 The metabolism and clearance of TCE and its toxic metabolites have been
32 examined by various studies. Although there is no study that has addressed the clearance
33 of TCE in children, the clearance of the toxic metabolite chloral hydrate is reduced in the
34 child. Also, from what is known from the metabolism of xenobiotics in the fetus and
35 newborn, most of the major enzymes responsible for the metabolism of TCE and its
36 metabolites are reduced in the fetus as compared to the adult. The reduced
37 metabolism/clearance for many pathways continue through the newborn period and into
38 infancy. Since the toxic effects of TCE and the metabolites are dose-dependent, the best
39 indication is that TCE itself and chloral hydrate or TCOH are probably all toxic and have
40 decreased clearance in the developing human, placing the child at increased risk. The
41 metabolism of TCOH in the premature newborn has been shown to be decreased by as
42 much as 5-fold and this compound is considered to be more toxic than some of the parent
43 compounds. The decreased enzyme activity would include at least the following
44 important enzymes: P450 2E1, ADH, Glucuronidation, and P450 1A2 (fetus, newborn,
45 and infant). In addition, renal clearance of phase II products is decreased in the fetus and
46 newborn. Finally, it is known that the enterohepatic circulation of glucuronidated

1 substrates such as bilirubin is enhanced in the newborn resulting in increased body
2 burdens of glucuronidated substrates excreted into the biliary tree.

3
4 Another major area of concern is TCE-related adverse effects. Neurobehavioral
5 toxicity may be the most important for the general population. The Panel notes, from
6 animal studies of TCE and its metabolites, that the developing rodent may be more
7 susceptible to altered neurobehavioral function as discussed above. The only
8 developmental neurotoxicity study of TCE is the Taylor et al (1985) study, which did not
9 compare dosing during adulthood with gestational dosing and which did not report
10 sufficient data to be able to determine a LOAEL in mg/kg. There is a Moser et al (1999)
11 neurotoxicity study of DCA which compared adult dosing with dosing of weanlings and
12 found increased susceptibility in the young, but it is unlikely that the levels of DCA
13 associated with developmental neurotoxicity would be achieved with even very high
14 exposures to TCE. Thus, there are not sufficient data to conclude that the central nervous
15 system of the developing organism is more sensitive to the effects of TCE than is the
16 adult central nervous system. This is clearly an important research need. Taylor (1985)
17 looking at TCA found the observed neurobehavioral effects may be permanent, if the
18 exposure occurred throughout gestation through weaning, unlike other studies in adults
19 where the effects were transient.

20
21 There are no neurodevelopmental studies examining the offspring of children
22 born to mothers exposed to TCE in the workplace. Also there are no neurobehavioral
23 studies comparing children exposed to drinking water with different levels of TCE. These
24 studies would be most difficult and expensive to conduct, but should be conducted in
25 order to assess the neurobehavioral risk of the child to TCE more accurately.

26
27 In general, the finding that the developing mammal, including the human, is more
28 susceptible during development to central nervous system toxic chemicals is generally
29 well accepted. This is easily shown with ethanol in the Fetal Alcohol Syndrome seen in
30 children exposed to ETOH in utero, and also with mercury intoxication and PCB
31 exposure. The effects for example in Fetal Alcohol Syndrome are not only dramatic but
32 also life-long. TCE and its metabolites are mostly likely going to cause greater harm in the
33 child than the adult, and the harm may even cause permanent alteration in children. In
34 fact, the human newborn has prolonged central nervous system effects from chloral
35 hydrate exposure, as compared to the adult.

36
37 There are other toxicities of concern, such as birth defects (cardiac, eye, and
38 central nervous system⁴), endocrine disruption, hepatic toxicity, immune dysfunction, and
39 cancer. In the human newborn, it has been shown that chloral hydrate causes hepatic
40 dysfunction after a few weeks of exposure. In regard to birth defects, there are animal and
41 human population data that suggest that TCE may be associated with these birth defects,
42 but there are conflicting data from other studies that do not support these findings. In

⁴ The Panel notes 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 was based largely on central nervous system effects in healthy adults and did not address the potential greater sensitivity of children.

1 addition, children may have increased susceptibility to certain cancer. It would be helpful
2 in the draft assessment to discuss these preliminary conclusions in greater detail. An area
3 of concern that has not been addressed in any developmental study is endocrine
4 disruption. This is a potentially important area that may have significant impact. All of
5 these concerns demonstrate increased uncertainty and areas where more research is
6 needed. In addition, more research is needed to determine whether toxicities to these
7 organ systems occur in developing mammals at lower doses than in adults. The relevant
8 questions concerning susceptibility are not only whether toxicities to these organ systems
9 occur in developing mammals, but also whether they occur at lower doses than in adults.
10 The data on TCE are too limited to conclude either way.

11
12 Another great area of concern is cumulative risk and in particular exposure to
13 alcohol during gestation. The potential for chemical-to-chemical interaction between
14 TCE and ETOH resulting in greater toxicity of both to the human fetus is substantial and
15 should be carefully addressed in the draft assessment.

16
17 In summary, the developing mammal, including the human, may be at greater risk
18 from TCE than the adult. It would be a worthwhile effort to try to quantitate the potential
19 differences observed in clearance, body burdens, and susceptibility. This task is very
20 difficult to accomplish, since the clearance and toxicity of the TCE is different from the
21 metabolites. Despite these difficulties it would be a worthwhile exercise.

22 23 10.2.3. How the Draft Assessment Can Be Improved

24
25 Overall, the review draft assessment is well prepared. The data on the children
26 are presented throughout the draft assessment. This is appropriate, but the overall review
27 and understanding of the children's issues would be greatly improved if the overall
28 toxicokinetics and toxicodynamics would be sequentially discussed in one section and the
29 draft assessment included a comprehensive chapter on children.

30
31 A discussion of the various adverse outcomes (cancer, neurobehavioral
32 dysfunction, cardiac anomalies, endocrine disruption and liver toxicity) and the potential
33 mechanism of action need to be discussed for TCE and each of the metabolites. It is
34 possible or even likely that there is not one mechanism of action, but many. It is possible
35 that due to altered metabolism during development that the potential toxicity mechanisms
36 may change.

37
38 It would be helpful for the Agency to discuss the toxicokinetics and
39 toxicodynamics for each metabolite and the effects of action on the metabolism,
40 clearance, adverse effects, and mode of action. The Panel advises the Agency to examine
41 how age would alter the kinetics and dynamics and how TCE and the metabolites can
42 interact with one another. There is a large amount of information for chloral hydrate that
43 was not fully discussed.

44
45 The other issue is cumulative risk. A discussion of potential interaction with
46 maternal alcohol intake and other chemicals would be helpful.

1
2 One area needing further clarification in the draft assessment is related to the
3 timing of exposure to TCE during development. It is important to identify exposure
4 scenarios through various routes and doses to the developing and growing fetus/child.).
5 Given that mean exposure to TCE in the urban air is at about 0.3 ppb and water
6 contamination is at 50 ug/L or less (Wu et al. 2000) and that Agency for Toxic
7 Substances and Disease Registry estimates that up to one-third of drinking water supply
8 sources have some TCE contamination (ATSDR, 19??), and if and how prenatal exposure
9 to these levels is likely to be of concern. Further, what, if any, are the implications of fat
10 storage during pregnancy and then mobilization of the fat during the last trimester.
11 Exposures to the fetus and neonate, given these potential internal sources of exposure and
12 given the considerable pharmacokinetic and pharmacodynamic uncertainty for children,
13 need more detailed estimations. Breast milk exposure is of special concern, since TCE is
14 lipophilic and is measured in breast milk. The question of a child's body burden, given
15 these multiple exposures needs to be estimated. The footnote on page 1-15 of the draft
16 assessment provides a critical example how the various scenarios could be developed
17 showing the unit risk for water consumption of 3.9.

18
19 Regarding additional research needed, the Panel recommends that a study be done
20 to evaluate the body burden of newborns and infants who are likely exposed due to air
21 and/or water contamination. This may be accomplished via a combination of breath,
22 urine, and possibly occasional blood sampling.

23
24 The uncertainty is very high due to lack of data. Critical studies on longitudinal
25 studies after intrauterine and new born/infant exposure have not been done. Of particular
26 concern are neurobehavioral effects, endocrine function, reproductive function, birth
27 defects and cancer. These studies will have to be completed in the human to improve the
28 overall risk assessment for children.

29
30 The key studies should be discussed at greater depth and length. Finally, when
31 children's risks are discussed, the pharmacokinetics and pharmacodynamics of the parent
32 compound and the metabolites for the pregnant female would improve the overall
33 evaluation of the study.

34
35 In regards to cancer, the draft assessment would be improved with a discussion
36 and examination of vinyl chloride exposure during development and cancer. In
37 particular, the draft assessment might benefit with a comparison to potential TCE cancers
38 in children, by comparing sensitivity and expression of the induced cancers.

39
40 One last comment regarding this and other EPA draft assessments, which state
41 that children generally metabolize chemicals faster. This is not true generally and, for
42 example, in the fetus and newborn and well into infancy, it is rarely true. A general
43 statement cannot be made.

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APPENDIX A

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

1 Prevention, the Hanford Health Effects Subcommittee for ATSDR and is a member of the
2 NIOSH Advisory Board on Radiation and Worker Health. He is a fellow of the
3 Collegium Ramazzini and the American Association for the Advancement of Science.
4 He is associate editor of the American Journal of Industrial Medicine and serves on the
5 editorial board of Cancer Prevention International.

6
7
8 Blair, Aaron: National Cancer Institute, National Institute of Health
9

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

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

45 He has served on Editorial Boards of the American Journal of Epidemiology,
46 Scandinavian Journal of Work, Environment and Health, and the Journal of Agricultural

1 Safety and Health. Dr. Blair is a member of the American Epidemiologic Society and a
2 Fellow and Board Member of the American College of Epidemiology.

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

6
7
8 Borghoff, Susan J.: CIIT Centers for Health Research

9
10 Dr. Susan Borghoff has been a Staff Scientist at CIIT Centers for Health Research
11 in the Research Triangle Park, North Carolina since 1989 following her postdoctoral
12 fellowship. Prior to her position at CIIT, Dr. Borghoff was a graduate student at the
13 University of North Carolina and conducted her research at the National Institute for
14 Environmental Health Sciences (NIEHS). Along with Dr. Borghoff's research program at
15 CIIT she is also the Director of Education Programs which involves oversight of the pre-
16 to post- graduate training programs and K-12 educational outreach activities. Her
17 research interests have focused on understanding the mode-of-action by which specific
18 chemicals cause kidney toxicity and cancer in rats with a view to understanding the
19 relevance of this response for human risk assessment. Her research has also focused on
20 understanding the metabolism and pharmacokinetics of various chemicals with emphasis
21 on the development of physiologically based pharmacokinetic models that can be used
22 for risk assessment. Currently Dr. Borghoff's research is focused on the developmental
23 pharmacokinetics of estrogen-like compounds such as genistein. CIIT Centers for Health
24 Research is a not-for-profit research institution in which the major core funding is a grant
25 from the American Chemistry Council Long-Range Research Initiative. Other financial
26 support comes from government agencies (U.S. Environmental Protection Agency
27 (USEPA) and NIEHS), independent research organizations, trade associations, and
28 corporations. Dr. Borghoff's research projects have been funded both by the Core
29 research program and through specific research grants from Oxygenated Fuels
30 Association, American Petroleum Institute, American Chemistry Council and ARCO
31 (now Lyondell) Chemical Company. She has recently accepted an opportunity to consult
32 for Huntsman Chemical Company which involves conducting a literature review on what
33 is known on the health effects of methyl tertiary butyl ether.

34
35
36 Edler, Lutz: German Cancer Research Center

37
38 Dr. Edler is the Head of Biostatistics at the Research Programme Genome
39 Research and Bioinformatics of the German Cancer Research Center in Heidelberg
40 Germany. He holds a Dipl. Math (M.S.) Mathematics, Physics from the Albert-Ludwigs-
41 University, Freiburg, FRG and a Dr. rer. nat (Ph.D.) Mathematics from Johannes-
42 Gutenberg-University, Mainz, FRG. His major areas of research are: Mathematical-
43 statistical modeling of carcinogenesis and risk assessment; Pharmacokinetics and
44 development of methodology for clinical oncology with a strong emphasis on the
45 application computational statistics; Statistical Computing; Biostatistical Methods in

1 Design and Analysis of Experiments; Mathematical and Statistical Modeling in
2 Oncology; and Survival Analysis and Clinical Trials.

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

6 He has listed the following "Expert Meetings" in which he has participated:
7 (1994) DAAD, Bad Godesberg; (1994) Human PBPK Models for TCDD, NIEHS,
8 Research Triangle Park, USA; (1994, 1998) EUROSTAT, Luxembourg; (1998) Risk
9 Assessment of Electromagnetic Waves, US NIEHS, Tucson, AZ, USA; (2000) Risk
10 Assessment of Dioxin, US EPA, Fort Collins, USA; 5th Framework Program, EU,
11 Brussels; (1998) Rapporteur at EMF Science Review Symposium of the NIEHS,
12 Phoenix, AZ; and (2002) Working Group of US-Vietnam Scientific Conference on
13 Human Health and Environmental Effects of Agent
14 Orange/Dioxins, March 2002, Hanoi, Rep Vietnam.

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

21 Professional Activities include: (1991-1995) Scientific Secretary International
22 Association for Statistical Computing (IASC); (1995-1997) Vice President of the
23 International Association for Statistical Computing (IASC); (1999 -2001) President of the
24 International Association for Statistical Computing (IASC); (1993-1997) Member of the
25 Council of the German Region International Biometric Society; (1998-2002) Member of
26 the Council of the International Biometric Society; and (1993- now) Member of the
27 Animal Protection Commission at the RegPr. Karlsruhe. Currently he is 2002 Co-
28 Organizer of the Session "Clinical Trial" at the International Biometric Conference,
29 Freiburg, Germany; 2002 Coorganizer of the Session "Pharmacogenetics and
30 Pharmacogenomics Data Analysis Methods in Future Clinical Trials", 38th DIA Annual
31 Meeting, Chicago; 2003 Chair of the International Organizing Committee of the
32 International Conference on Carcinogenesis Risk Assessment (ICCRA), Athens, Greece;
33 and 2004 Co-Chair of the Local Organizing Committee of the Biometrical Colloquium of
34 the German Region of the International Biometric Society, Heidelberg, Germany.

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

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

1 Committee for Boehringer Mannheim Co.; and Reviewer for the German Cancer Society
2 and Krebshilfe.

3 Currently his editorial tasks include: (since 1993) Associate Editor of
4 Computational Statistics and Data Analysis (CSDA) and Associate Editor of
5 ONKOLOGIE; (since 1994) Associate Editor of the Biometrical Journal (Biometrische
6 Zeitschrift); (since 1999) Associate Editor of Journal of Cancer Research and Clinical
7 Oncology; and (since 2002) Editor of the Virtual Online Journal "Biostatistics" (Elsevier,
8 Publ.)
9

10
11 Hattis, Dale: Clark University (Current member, SAB Environmental Health Committee)
12

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

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

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

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

41 He has been a councilor and is a Fellow of the Society for Risk Analysis and
42 serves on the editorial board of its journal Risk Analysis. He holds a Ph.D. in Genetics
43 from Stanford University and a B.A. in biochemistry from the University of California at
44 Berkeley.
45
46

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

3
4 David G. Hoel, Ph.D., is a Distinguished University Professor at the Medical
5 University of South Carolina. Dr. Hoel received his A.B. degree in Mathematics and
6 Statistics from the University of California at Berkeley and his Ph.D. from the University
7 of North Carolina at Chapel Hill and has more than 25 years of experience as a
8 biostatistician, toxicologist and environmental health researcher.

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

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

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

37
38
39 Lambert, George: Robert Wood Johnson Medical School/ University of Medicine and
40 Dentistry of New Jersey (Current member, SAB Environmental Health Committee)

41
42 Dr. Lambert is Associate Professor of Pediatrics, Director Division of Pediatric
43 Pharmacology and Toxicology at the University of Medicine and Dentistry of New
44 Jersey, Robert Wood Johnson Medical School – Piscataway/New Brunswick. He is also
45 the Director of the NIEHS/EPA Center for Childhood Neurotoxicology and Exposure
46 Assessment, which is located at the Environmental and Occupational Health Sciences

1 Institute, a jointly sponsored institute of Rutgers, The State University of New NJ and
2 UMDNJ-Robert Wood Johnson Medical School

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

5 Recent grants and other outside funding sources include the following: (1) a grant
6 to study the Reproductive Outcomes of the World Trade Center Tragedy (funded by
7 National Institute of Environmental Health Sciences) (2) a grant to determine the
8 influences of environmental exposure to neurotoxicants on child neurological health and
9 development with special emphasis on autism and related disabilities (funded jointly by
10 the National Institute of Environmental Health Sciences and the Environmental
11 Protection Agency) (3) a grant to study the effects of Herbal Phytoestrogens & Prostate
12 Cancer (funded by the Cancer Commission of New Jersey); (4) Effects of eating Crabs
13 with PCBs and Dioxin Laden on Human Health (funded by the New Jersey Department
14 of Environmental Regulations); (5) a grant to study the role of gene polymorphisms in
15 Birth Defects. (funded jointly by the Centers for Disease Control and the NJ State Birth
16 Defects Registry); and (6) the correlation between hypospadiasm and xenoestrogens
17 (funded jointly by the Centers for Disease Control and the New Jersey Department of
18 Health).

19
20
21 Lemasters, Grace: University of Cincinnati (Current member, SAB Environmental
22 Health Committee)

23
24 Dr. Lemasters is a Professor in the Division of Epidemiology and Biostatistics
25 Department of Environmental Health, College of Medicine, University of Cincinnati and
26 former head of Epidemiology and Biostatistics in the Department of Environmental
27 Health, College of Medicine.

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

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

38 She has conducted research on men and women in the military for over 15 years
39 examining the effects of exposures to fuels and solvents on cytogenetics, female
40 hormones, male reproduction and neurological effects. Other areas of research include a
41 15-year pulmonary longitudinal study of the health effects of refractory ceramic fiber
42 exposure (substitute for asbestos) and lung cancer and lung disease. She has recently
43 received funding as the principle investigator on a 5-year study on diesel exposure and
44 atopy and respiratory disorders in children. Other current research includes the
45 following: caffeine effects on female hormones during early pregnancy, occupational

1 risk factors related to falls, and exposures of women in the military to jet fuel and
2 hormonal changes.

3 Among her service on Committees and Associations she lists: Federal Advisory
4 Committee on Children's Health NICHD (2002-); Armed Forces Epidemiological Board
5 (2001-present); Reviewer Department of Defense PRMRP (July 11-13, 2001; Member
6 National Toxicology Program Board of Scientific Counselors of the Office of the
7 Assistant Secretary and Surgeon General (1999-2002); Editorial Board: Occupational and
8 Environmental Medicine (1996-2001); Editorial Board: Journal of Reproductive
9 Toxicology (1991-); Fellow, American College of Epidemiology; Member, Society for
10 Epidemiology Research; and Member: Sigma Theta Tau Alpha and Beta Honors
11 Chapters.

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

15
16
17 Li, Abby: Monsanto Company (Current member, SAB Environmental Health
18 Committee)

19
20 Dr. Abby Li received her Ph.D. from the University of Chicago in pharmacology
21 and physiology. She is currently a Senior Science Fellow at Monsanto. She is a
22 toxicologist in the Department of Toxicology and Human Health Risk Assessment. She
23 has specialized expertise in neurotoxicology as well as product stewardship
24 responsibilities involving general toxicology, exposure and risk assessment issues. Dr. Li
25 has conducted numerous studies primarily for regulatory submission in neurotoxicology
26 in adult and developing rats, in humans and in vitro systems.

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

45
46

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

3
4 Dr. Ulrike Luderer is Assistant Professor of Medicine in the Division of
5 Occupational and Environmental Medicine at the University of California at Irvine. She
6 also holds joint appointments in the Departments of Developmental and Cell Biology and
7 Environmental Toxicology. Dr. Luderer's research focuses on mechanisms of action of
8 reproductive toxicants and on protective mechanisms against those toxicants. She is a
9 recipient of a National Institute of Environmental Health Sciences research grant (2002-
10 2007) entitled "Glutathione:Protecting Ovarian Follicles from Oxidant Injury" and a co-
11 investigator on an EPA grant "Latent Effects of Gestational Exposure to Heptachlor" She
12 has published peer-reviewed journal articles and book chapters and presented research at
13 national and international scientific conference on such topics as the effects of toluene
14 exposure on reproductive endocrine function, the functions of and regulation of
15 glutathione in the ovary, the differential regulation of follicle-stimulating hormone and
16 luteinizing hormone secretion, and reviews of reproductive and developmental and
17 endocrine toxicology. She has served on the National Toxicology Program/NIEHS
18 Center for the Evaluation of Risks to Human Reproduction Expert Panel on 1- and 2-
19 Bromopropane and on the National Research Council subcommittee on methyl bromide.
20 She is currently member of the EPA SAB's Environmental Health Committee. Dr.
21 Luderer has a Ph.D. in reproductive endocrinology and an M.D. from Northwestern
22 University and is board-certified in Internal Medicine and in Occupational and
23 Environmental Medicine. She has a Sc.B. in biomedical engineering from Brown
24 University.

25
26
27 McClain, Michael: McClain Associates

28
29 Dr. R. Michael McClain is currently an Adjunct Professor University of Medicine
30 and Dentistry of NJ and now works primarily as a consultant in toxicology. He was
31 formerly a Distinguished Research Leader and Director of Toxicology, Hoffmann-La
32 Roche, Inc. Dr. McClain received his Ph.D. from the Department of Pharmacology at the
33 University of Iowa and B.S. and M.S. degrees from Duquesne University. Dr. McClain
34 is a Diplomate of the American Board of Toxicology and a Fellow of the Academy of
35 Toxicological Sciences. He has worked in the pharmaceutical industry for over 30 years
36 in the areas of teratology and reproductive toxicology, general toxicology and
37 carcinogenicity testing. His research activities are involved primarily in mechanisms of
38 chemical carcinogenesis for thyroid, liver and adrenal and regulatory aspects for cancer
39 risk assessment. He has been active in the Pharmaceutical Research and Manufactures
40 Association and PhRMAs efforts on harmonizing international guidelines for drug
41 development (ICH). He has been involved with the ILSI organization and served as
42 President of the ILSI's Health and Environmental Science Institute (HESI) and as a
43 member of ILSI's Board of Trustees. Dr McClain is a member of the National Advisory
44 Environmental Health Sciences Council for NIEHS. Dr. McClain is also active in the
45 Society of Toxicology having served a term as Treasurer and as President of the Society
46 in 1998

1
2
3 Melnick, Ronald: National Institute of Environmental Health Sciences
4

5 Dr. Melnick is a Senior Toxicologist and Director of Special Programs in the
6 Environmental Toxicology Program at the National Institute of Environmental Health
7 Sciences (NIEHS), National Institutes of Health in Research Triangle Park, North
8 Carolina. Prior to this position he was Group Leader of the Toxicokinetic and
9 Biochemical Modeling Group in the Laboratory of Computational Biology and Risk
10 Analysis at NIEHS. Dr. Melnick obtained his B.S. degree from Rutgers University and
11 his Ph.D. in food science/biochemistry from the University of Massachusetts at Amherst.
12 He was a postdoctoral research fellow in the Department of Physiology-Anatomy at the
13 University of California in Berkeley and then an assistant professor of life sciences at the
14 Polytechnic Institute of New York. At NIEHS he has been involved in the design,
15 monitoring and interpretation of NTP toxicity and carcinogenesis studies, as well as
16 mechanistic studies to characterize the behavior of environmental carcinogens. He spent
17 one year as an agency representative to the White House Office of Science and
18 Technology Policy to work on interagency assessments of health risks of environmental
19 agents and on risk assessment research needs in the Federal government. Dr. Melnick
20 has organized several national and international symposiums and workshops on health
21 risks associated with exposure to environmental and occupational toxicants. He has also
22 served on numerous scientific review and advisory panels, including the working group
23 of the International Agency for Research on Cancer (1995) that classified
24 trichloroethylene as probably carcinogenic to humans. Dr. Melnick has served on several
25 committees at NIEHS, including Chair of the Toxicokinetic Faculty and member of the
26 NIEHS review group for the NTP Report on Carcinogens. The latter group reviewed
27 data on trichloroethylene for listing in the Report on Carcinogens. Dr. Melnick is a
28 Fellow of the Collegium Ramazzini. As a federal employee, he does not receive any grant
29 or contract support.
30

31
32 Solomon, Gina: Natural Resources Defense Council
33

34 Dr. Gina Solomon is a Senior Scientist at the Natural Resources Defense Council
35 in San Francisco and an Assistant Clinical Professor of Medicine at the University of
36 California at San Francisco. Dr. Solomon is a specialist in internal medicine, preventive
37 medicine, and occupational and environmental medicine. Her work has focused on
38 environmental and occupational threats to reproductive health and child development.
39 She attended medical school at Yale and underwent post-graduate training in medicine
40 and public health at Harvard. Dr. Solomon served on the U.S. EPA's Federal Advisory
41 Committee on endocrine disrupting chemicals and is a scientific advisor to numerous
42 organizations including the California Department of Health Services Environmental
43 Epidemiology Section and the Pediatric Environmental Health Specialty Unit at U.C. San
44 Francisco. Dr. Solomon has published peer-reviewed articles on various topics, including
45 solvents and miscarriage, endocrine disruptors, diesel exhaust and asthma, and

1 contaminants in breast milk. She is a co-author of the book, Generations at Risk:
2 Reproductive Health and the Environment, published by MIT Press in 1999.

3
4
5 Whyatt, Robin: Department of Environmental Health Sciences

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

40
41
42 Yang, Raymond: Colorado State University,

43
44 Raymond S. H. Yang is presently Professor of Toxicology and Director of Center
45 for Environmental Toxicology and Technology, one of 14 Programs of Research and
46 Scholarly Excellence at Colorado State University (CSU). Between July 1990 and June

1 1995, Dr. Yang served as the Head, Department of Environmental Health, College of
2 Veterinary Medicine and Biomedical Sciences, CSU, Fort Collins, CO. Prior to joining
3 CSU in 1990, Dr. Yang spent seven years each in chemical industry (Bushy Run
4 Research Institute, Union Carbide - Mellon Institute, 1976 - 1983) and in the federal
5 government [National Institute of Environmental Health Sciences/National Toxicology
6 Program (NIEHS/NTP), 1983 - 1990].

7 Dr. Yang received his B.S. in Biology from the National Taiwan University in
8 1963; M.S. and Ph.D. in Toxicology/Entomology from North Carolina State University
9 in 1967 and 1970, respectively. Between 1970 and 1973, he was a postdoctoral fellow at
10 Cornell University. Between 1973 and 1976, he was Research Associate and then
11 Assistant Professor at the Institute of Comparative and Human Toxicology, Albany
12 Medical College. Dr. Yang had also been appointed Adjunct Associate Professor at
13 University of Pittsburgh and Adjunct Professor at North Carolina State University.

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

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

1 APPENDIX B

2 SPECIFIC PANEL COMMENTS ON THE AGENCY'S ASSESSMENT OF
3 NONCANCER ENDPOINTS
4

5 1. Specific Comments on Hazard Characterization for Noncancer Endpoints
6

7 This section considers whether the draft assessment adequately characterizes the
8 data at each site of toxicity.
9

10 1.1. Liver Effects
11

12 This endpoint requires significant attention because the liver weight to body
13 weight change (LW/BW) is the key endpoint used to establish the oral RfD. There are
14 scientific data available on mode of action, species differences, case studies (both
15 positive and negative) following oral ingestion, severity of effect, and the relationship
16 between effect and duration of exposure that can greatly inform the selection of
17 uncertainty factors. The Panel advises the Agency to include a critical evaluation of the
18 key studies used for determining the oral RfD [e.g. Tucker et al., (1972), Buben and
19 O'Flaherty (1985), Berman (1995)] in this section would be helpful to discuss the
20 quantitative changes in LW/BW ratios and to determine if the National Toxicology
21 Program (NTP) toxicology and carcinogenesis studies of TCE in four strains of rats (CAS
22 No. 79-01-06) reports any LW/BW changes either in the report or raw data base and how
23 these changes relate to liver histopathology. Understanding how effects on LW/BW
24 progresses relative to duration to exposure will provide a scientific basis for extrapolating
25 from subchronic to chronic exposures
26

27 The Agency's discussion of this endpoint refers to the state-of-the-science reviews
28 by Bull (2000) and Barton and Clewell (2000) that summarize the effects of TCE, TCA,
29 DCA and CH on increased liver size, but fails to also include the discussions on
30 relevance of these findings to TCE toxicity based on the dose level and cytotoxicity. As
31 discussed in the general comments, it would be helpful to accompany any discussion of
32 metabolites, where possible, with a more quantitative critical evaluation of the data.
33

34 The Agency's discussion of this endpoint mentions the results of several animal
35 studies that examined the hepatotoxicity of metabolites of TCE. Human studies that have
36 examined hepatotoxicity associated with TCE metabolites or with compounds that have
37 the same metabolites, such as PCE, should also be summarized and quantitatively
38 analyzed here. An example is the study by Brodtkin et al. (1995) that found significant
39 hepatic ultrasound abnormalities in dry cleaning workers exposed to PCE, even in the
40 absence of significant effects on routine liver function studies. Such a review should
41 include a discussion of exposure levels.
42

43 Sub-section 3.4.2.2 of the draft assessment refers to Tier I, II, III studies, but the
44 meaning of these terms is not explained until later in the text (footnote 46 to Section
45 3.6.2). The footnote should be moved to the first mention of the terms.
46

1 1.2. Kidney Effects
2

3 For TCE, the Agency notes that an RfD can be based on critical effects in the
4 liver, kidney and developing fetus. There is very little information presented in the draft
5 assessment (section 3.4.3.1) describing the kidney toxicity that was stated to occur in
6 humans exposed to TCE and in rodents. There should be a more thorough summary of
7 the human toxicity studies since some are negative and some report changes in urinary
8 proteins reflective of damage. This does not come across in this draft assessment. It
9 appears the RfD review was based on the kidney effects reported by Maltoni et al.,
10 (1986) where the specific effects in the kidney were not described in any detail in this
11 draft assessment. Going back to this original study it appears that Sprague-Dawley rats
12 were dosed orally for 52 weeks and then followed until natural death. The response of
13 kidney meganucleocytosis was only observed in male rats at 250 mg/kg. It is not clear
14 from what is presented in the Maltoni publication or in the draft assessment as to whether
15 this lesion is associated with normal aging and is a response from chemical exposure.
16 There is an NTP report (1983: NTP TR 243) which reports karyomegaly of the renal
17 tubular cells in male rats at 2000 mg/kg TCE and female rats at 1000 mg/kg TCE (13
18 week study). The Panel advises the Agency to reevaluate both of these studies and their
19 findings prior to setting of the kidney NOAEL. It is also not clear why the Berman et al
20 (1995) paper was not used by either Barton and Clewell or in the draft assessment to
21 derive a LOAEL for kidney toxicity of 50 mg/kg/d with 14 day dosing. This would have
22 lowered the human effective dose (HED) for nephrotoxicity and should therefore be
23 explicitly addressed in the draft assessment.
24

25 1.3. Developmental Effects
26

27 The draft does discuss multiple effects on children and the developing fetus. The
28 draft assessment discusses the evidence that TCE may be a cardiac (and possibly
29 ophthalmologic) teratogen. This issue deserves greater attention and critical analysis.
30 Cardiac teratogenesis has been reported in community-based epidemiological studies in
31 which TCE was a contaminant. Four studies in the rat model (on TCE, TCA and DCA)
32 have revealed significant excesses of cardiac defects. A relatively recent mechanistic
33 study using chick embryos cultured on collagen gel (Boyer et al. 2000) has identified a
34 possible mode of action by which TCE may cause cardiac defects – dose dependent
35 inhibition of mesenchymal cell transformation. A more recent study by Fisher et al,
36 (2001) failed to identify cardiac defects in the rat. Differences between this study and the
37 other studies should be evaluated relative to sample size route of dosing, duration and
38 timing of exposure, maternal toxicity, and relevance to humans.
39

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

1 studies of the TCE metabolites, TCA and DCA, should be summarized separately and
2 evaluated as to their consistency with the TCE studies and pharmacokinetics of TCE.

3
4 The Panel advises the Agency to discuss the strengths and weaknesses of the
5 studies, based on dose levels compared to relevant occupational and environmental
6 exposure levels, and based on relevance of methods used (e.g. chick embryos cultured on
7 collagen gel; osmotic mini pumps delivering TCE directly to the uterine lumina). The
8 section could be improved by discussing more several negative developmental studies
9 that used inhalation exposure to TCE at relevant exposure levels. These studies are not
10 referenced individually, but rather the reader is referred to Barton and Clewell (2000)
11 [the actual referenced papers are Healy et al.(1982); Dorfmueller et al. (1979); Hardin et
12 al; (1981); and Schwetz et al. (1975)]. These negative as well as the positive studies
13 should be summarized and critically evaluated. Special attention should be given to the
14 Fisher et al. (2001) paper which used 19-20 litters, high oral gavage doses, exposure
15 duration of GD 6-15 which spans the critical periods of heart development in rats, and
16 sensitive techniques conducted blind in collaboration with an investigator who initially
17 detected an effect in an earlier study (Johnson et al., 1998).

18
19 At times, the draft assessment makes overgeneralizations that make detailed and
20 specific interpretations difficult. One specific example is in section 3.4.4.2. One study
21 (Cohn et al., 1994) is reported related to childhood leukemia with an “observed very
22 strong association” with exposure during pregnancy and an exposure response gradient
23 with drinking water contamination as the etiologic agent with TCE “often the chemical
24 found in highest concentration.” Though the odds ratio is 13.2, the confidence interval
25 includes 1 ranging from 0.9 to 205.2. Thus, the significance of this finding may be over-
26 stated.

27 28 1.4. Neurotoxicity Effects

29
30 Several of the critical studies in Table 4-3 for neurotoxicity are human
31 occupational studies. The Panel advises the Agency to discuss whether the subjects had
32 other exposures besides TCE. For example, the study by Rasmussen et al. included
33 workers with concomitant exposures to CFC113 as well as other unspecified solvents.
34 The Arito et al. (1994) study was not discussed in Section 3.4.1. and should be discussed
35 because it may be one of the most sensitive endpoints for setting RfCs based on
36 neurotoxicity.

37
38 The text in section 3.4.1 refers to a study by Moser et al. from 1999 that used
39 DCA as the test substance but does not discuss the dose-response relative to quantitative
40 levels of DCA following TCE exposure to rats and to known relevant human exposure
41 levels. This type of discussion is essential in order to understand the relevance of these
42 studies to the TCE risk assessment. It is unlikely that DCA plays a role in TCE
43 neurotoxicity, based on the discussions in the state-of-the-science papers (Lash et al.,
44 2000; Barton and Clewell, 2000). The 1995 paper by Moser et al. that tested the
45 neurobehavioral effects of 1- and 14-day exposures to TCE (referenced in Table 4.2),
46 among other compounds, should be discussed in section 3.4.1. and included in the

1 reference list. The Boyes et al. (2000) paper studying acute peak vs. repeated exposure,
2 and the Moser et al. (1995) comparison of 1 and 14-day exposure should be evaluated in
3 terms of providing information in extrapolation from shorter to longer duration
4 exposures.

6 1.5. Endocrine System Effects and Reproductive Toxicity Effects

8 The relevant section of the draft assessment needs to be discussed more carefully
9 because endocrine effects raise particular concerns for potential effects on the developing
10 fetus, including concerns about vulnerable life stages that should be considered in the
11 discussion about uncertainty factors and children's vulnerability. Therefore it is
12 important that a more critical evaluation and balanced presentation of the data be given in
13 this section. Additional specific comments on the human endocrine toxicity studies used
14 in the derivation of the RfC are provided in section 6.2.5 of the draft assessment. Both
15 negative and positive data should be reported including the results of the 2-generation
16 reproductive studies with mice and rats using microencapsulated TCE in feed discussed
17 in the state-of-the-science review by Barton and Clewell (2000).

19 In terms of reviewing the epidemiological literature, section 3.3.1.3 of the draft
20 assessment reports excess risks of cervical cancer in occupationally or environmentally
21 exposed women. More specific details of these studies are needed in order to bring
22 clarity to the discussion, as specifics of the actual study findings are sparse. The report
23 states "TCE exposure has been associated with excess risks of cervical cancer in
24 occupationally or environmentally exposed women (Blair, 1998; Anttila, 1997; and Burg,
25 1997 cited). These studies typically cannot account for possible confounding from
26 lifestyle factors. According to public comments provided to the Panel, the Anttila et al.
27 (1995) study found a significant increase in cervical cancer for women exposed to TCE
28 for less than ten years, but not for longer than 10. Blair showed non-significant but
29 elevated breast cancer mortality rate ratios in the low level intermittent or continuous
30 exposures (3.1-3.4) that were higher than those reported in those having frequent peaks
31 RR=1.4. In the Blair et al. study (1998), cervical cancers had rate ratios of 1.8, which was
32 not significant with confidence intervals of 0.5-6.5. Prostate cancers in men also were not
33 significant. A more thorough description of the actual findings, limitations and
34 implications is needed.

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

45 In an NTP CD-1 mice study a 45% and 18% reduction in sperm motility was
46 observed in the baseline and first generation of males, even though no effect was

1 observed on mating, fertility or reproductive performance. In contrast, the primary
2 finding of the Zenick et al. 1984 study on male rats showed that TCE-related effects were
3 seen primarily in the 1000 mg/kg group related to impaired copulatory behavior. The
4 copulatory functions had returned to normal by the fifth week of exposure and essentially
5 no effects on sperm parameters were observed. The conclusion from this latter study was
6 that “TCE exerts minimal direct effects on the male reproductive system in terms of
7 spermatotoxicity “, but TCOH showed a 3-7 fold increase in the testis, prostate, seminal
8 vesicle, fat, liver, kidney and lung. The Zenick et al. study demonstrates the ability of the
9 reproductive organs to concentrate TCE and its metabolites with increasing dose.

10 11 2. Specific Comments on Uncertainty Factors for NonCancer Endpoints

12 13 2.1. Human Variation

14
15 In the view of some panel members, the current draft assessment makes a
16 potential error in treating the pharmacokinetic uncertainty as if it were a measure of
17 human inter-individual variability. Pharmacokinetic variability in total metabolism may
18 be small; variability in the area under the curve of major metabolites could be more,
19 because of differences in elimination rates of things like TCA, and variability in
20 production and persistence of minor metabolites could be large. Others agreed with
21 EPA’s approach and recognized that interindividual variability in metabolism and
22 response to TCE is likely to be large, especially when children are considered. The El-
23 Masri (2000) analysis would appear to indicate that the data-derived factor for human
24 variation should actually be 625x. EPA's analysis would be strengthened by explaining
25 the range of data and methods available for assessing interindividual variability and
26 describing the rationale more clearly for the approach taken.

27
28 In addition, the known 3.5 - 5-fold difference between adults and infants for
29 metabolism of TCE should have been included in the EPA analysis. This could be
30 addressed by specific modeling of human variability distributions.

31
32 Pharmacodynamic variability is another matter. Different endpoints may be
33 causally related to different metabolites and different dosimeters related to those
34 metabolites [e.g. maximal concentration (Cmax) vs. area under the curve in relevant
35 locations in the body]. Therefore there may be different pharmacokinetic variability
36 “uncertainty factors” for different endpoints. This would be a useful question for future
37 research. A related issue concerns appropriate estimates of the pharmacokinetic portion
38 of human interindividual variability. The Panel encourages the Agency to explore
39 deriving them by exercising the various pharmacokinetic models using the population
40 variability of various pharmacokinetic parameters estimated by Bois, together with the
41 dependencies (a more general word than “correlations”) among the values of these
42 parameters. Obtaining these inputs for variability simulations may require and inquiry or
43 new consultation with Dr. Bois. Variability should be calculated separately for different
44 dosimeters putatively related to different adverse effects (e.g. areas under the curve vs.
45 peak levels of key metabolites hypothesized to be involved in causing specific effects).

46

1
2 Ultimately, the whole system of uncertainty factors could be usefully revisited
3 and defined in terms of an objective of achieving x level of risk for the yth percentile of
4 the variable human population with z degree of confidence.

5 6 2.2. Animal-to-Human Uncertainty 7

8 In regard to the RfD, the Agency's RfD is based on effects on LW/BW ratio. The
9 EPA document explores many different modes of action for TCE's effects on the liver.
10 The state-of-the-science papers (Bull, 2000, Barton and Clewell, 2000) critically and
11 quantitatively evaluate the likelihood of different modes of actions to be relevant. Barton
12 and Clewell conclude that LW/BW alterations involve peroxisome proliferator-activated
13 receptor (PPAR) and that the data do not support the standard default assumption that
14 humans are more sensitive than the most sensitive rodents. The EPA document also
15 acknowledges that humans in general have lower expression of PPAR alpha compared to
16 mice and that these "quantitative differences have import to the dose response analysis of
17 the mouse liver tumors. (Page 3-27). The EPA document should discuss this scientific
18 evidence in their discussion of the selection of uncertainty factors. If different endpoints
19 are used to derive temporary RfDs, as recommended by the EPA's SAB, then different
20 considerations should be made depending on the most likely modes-of-action
21

22 In regard to the RfC, and in light of the supportive data for effects at similar
23 exposure levels in the human studies, it seems appropriate to omit this factor.
24

25 2.3. Subchronic-to-Chronic Uncertainty 26

27 In regard to the RfD, several members of the Panel felt it was not appropriate to
28 apply uncertainty factor for subchronic-to-chronic effects based on other effects such as
29 the central nervous system, follicular stimulating hormone (FSH), testosterone, etc., on
30 the LW/BW endpoint, whereas other panelists thought that a standard ten-fold
31 subchronic- to-chronic uncertainty factor would be reasonable. It was unclear to the
32 panelists why a full ten-fold factor was used for subchronic-to-chronic in the derivation
33 of the RfC, but only a three-fold factor was used for the RfD. This point requires
34 clarification in the draft assessment. The Panel advises EPA to evaluate these endpoints
35 independently and compare with the RfD derived for that calculated for the liver
36 weight/body weight ratio and EPA enhance the discussion of the scientific rationale for
37 this uncertainty.
38

39 The liver endpoints bring up yet another issue, which is the definition of chronic.
40 The Tucker et al. (1982) study dosed mice for 6 months, a significant proportion of a
41 mouse's lifespan of 2 years, and could therefore be considered a chronic NOAEL, not
42 requiring adjustment. The Berman et al. study (1995) reported dose-dependent increases
43 in liver weight after 14 days of dosing, and the Buben and O'Flaherty (1985) study after
44 6 weeks of dosing. One would like to be able to assess whether the effect was greater in
45 the studies with longer dosing durations to support the use of an uncertainty factor for
46 subchronic-to-chronic adjustment for the two shorter studies. Unfortunately, the Tucker

1 et al. study did not report the liver weight values. Barton and Clewell (2000) argued that
2 changes in relative liver weight are early events that are sensitive indicators of potential
3 liver effects observed at later times, and therefore no adjustment should be made for
4 exposure duration. This argument would be supported if there were no evidence of
5 duration-response trends in liver weight or other aspects of liver toxicity.

6
7 The use of an uncertainty factor for sub-chronic to chronic dosing makes more
8 sense for some of the endpoints than others. As the draft risk assessment points out, there
9 is evidence for duration response trends for neurotoxicity from the human inhalation
10 exposure studies. Another interpretation is that there are fewer effects acute high
11 exposures, compared to longer duration exposure [Moser (2000) and Boyes et al. (2000)].
12 A standard 10-fold uncertainty factor should not be applied for the developmental
13 endpoints of the Dawson et al. (1993) and Narotsky et al. (1995) studies. The application
14 of uncertainty factors is somewhat endpoint-specific and combining uncertainties from
15 different endpoints may be difficult to justify scientifically.

16
17 In regard to the RfC, the Panel notes that the RfC includes a 10-fold factor for
18 subchronic-to-chronic. However studies cited were 16 years and 7 years exposure
19 duration. The draft assessment should explain how this might impact such a factor. The
20 Arito et al. neurotoxicity study was a 6-week study. Some panelists said that if duration-
21 response effects were observed in the supportive human neurotoxicity studies, it seems
22 appropriate to apply this factor to this study. For the liver weight effects observed in the
23 30 day Kjellstrand (1983) study similar arguments can be made as for the liver effects in
24 the oral dosing studies. Applying this factor should depend on whether there is any
25 evidence of duration-response trends for this endpoint. Other panelists supported the use
26 of a ten fold factor for subchronic-to-chronic and urged the Agency to also apply the full
27 ten fold factor to the RfD.

28 29 2.4. LOAEL to NOAEL Uncertainty

30
31 In regard to presentation and communication of the Agency's justification for
32 choosing NOAELs and LOAELs for the RfD, Table 4-2 needs to explicitly identify
33 which NOAEL/LOAEL goes with which effect. In Table 4-2, first row, the NOAEL of
34 18 mg/kg/d for males seems to be from the Tucker et al. (1982) study for liver weight,
35 not the Sanders et al. (1982) study as indicated in the table. In contrast, the 18-mg/kg/d
36 dose represents a LOAEL for cell-mediated immune response to sheep erythrocytes in
37 females from the Sanders et al. study. The 217 mg/kg/d NOAEL in males is identified as
38 coming from the Sanders et al. study, and seems to refer to the humoral response to sheep
39 erythrocytes after 6 months of TCE exposure. Other effects were seen in males at lower
40 doses, and it is not clear why those were not chosen as the critical effect. For example the
41 recruitment of peritoneal cells showed a dose-dependent decline with a LOAEL of 18
42 mg/kg/d in males at 4 months.

43
44 For several of the other parameters, there was not a clear dose-response in males.
45 The female NOAEL/LOAEL of 193 mg/kg/day could not be found in either of those
46 studies of 193 mg/kg/d. The NOAEL for liver weight in females in the Tucker et al.

1 (1982) study was 437 mg/kg/d according to the text. Tables 3 and 4 from Barton and
2 Clewell (2000), which is referenced as a source of the experimental doses listed in Table
3 4-2 of the TCE draft assessment, identify a NOAEL for immunotoxicity from the Sanders
4 et al. study as 200 mg/kg/d. This is because they discount the LOAEL of 18 mg/kg/d in
5 females for the cell-mediated response to Sheep Red Blood Cells and in male for
6 peritoneal macrophage recruitment. Barton and Clewell cite the difference between the
7 naïve and vehicle controls for the former and do not mention the latter. Regarding the
8 effect on peritoneal macrophage recruitment, Sanders et al. state that the vehicle control
9 levels in the males were higher than their historical controls, so that may be the reason for
10 not considering that a critical effect.

11
12 Use of the statistically significant effects that were observed in the Sanders et al.
13 study at 18 mg/kg/d as the critical effects would have resulted in a HED NOAEL for
14 immune effects of less than 1 mg/kg/d, so this is an important issue.

15
16 In Table 4-2, row 3, the 50-mg/kg/d dose is a LOAEL for liver weight and kidney
17 weight according to Table 4 of the original Berman et al. (1995) paper. The text and
18 Table 3 of the Berman paper list 150mg/kg/d as the LOAEL in the multivariate ANOVA,
19 which included serum liver function test values and liver histopathology, as well as liver
20 weight. Barton and Clewell (2000) considered 50 mg/kg/d to be a LOAEL for liver
21 toxicity in the Berman et al. study. It is not clear why the Berman et al. paper was not
22 used by either Barton and Clewell or in the draft assessment to derive a LOAEL for
23 kidney toxicity of 50 mg/kg/d with 14d dosing. This would have lowered the HED for
24 nephrotoxicity and should therefore be explicitly addressed in the draft assessment. The
25 Maltoni et al. study (1986) from which the HED in Table 4-2 is derived dosed male
26 Sprague-Dawley rats for 52 weeks and then followed the animals until their natural
27 deaths, so some recovery from nephrotoxicity might have occurred before the kidneys
28 were evaluated. In the Berman et al. study, female Fisher 344 rats were dosed for 14d and
29 the kidneys were evaluated the 24h after the last dose. Thus there were sex, strain, and
30 experimental differences between the two studies.

31
32 In Table 4-2, row 3, the 150 mg/kg/d dose is a NOAEL for neurotoxicity
33 following 14d of exposure by gavage (Moser et al., 1995). Interestingly, the neurotoxicity
34 of DCA, a metabolite of TCE, was found in another study by Moser et al. (1999) to be
35 significantly greater by the drinking water than the gavage route, to be duration-
36 dependent, and to be greater when dosing was started at weaning than in adulthood.
37 Although the latter study tested DCA rather than TCE, it raises considerable uncertainty
38 about the extrapolatability of the 150-mg/kg/d neurotoxicity NOAEL to chronic
39 situations, to susceptible subpopulations (the young), or to drinking water exposure (the
40 more relevant route in humans). The observation that, for chronic oral dosing with DCA,
41 bolus administration of the entire daily dose by gavage results in less toxicity than
42 gradual administration of the same dose over the 24 hour period in the drinking water
43 suggests that one should not assume that gavage dosing with TCE is equivalent to dosing
44 via the drinking water. This suggests a research need for direct comparison of the effects
45 of gavage and drinking water dosing with TCE on various critical endpoints.

46

1 The discussion above points out additional issues that EPA may need to consider.
2 However, the final decision on selection of endpoints should be based on the weight of
3 evidence and consistency of findings across well-conducted studies. For example, the
4 Berman et al. study was a research study designed to develop screening methods and
5 used 8-animals/dose group and exposure was only 14 days. Certain endpoints measured
6 in this study may have been better evaluated in other more robust subchronic studies.
7 Careful critical evaluation of the strengths and weaknesses of studies is essential in the
8 selection of key studies and critical endpoints. As mentioned in general comments,
9 tabulation of studies will go a long way towards making the EPA's decisions transparent
10 and help the EPA identify areas that require further discussion in the text.
11

12 In regard to presentation and communication of the Agency's justification for
13 choosing NOAELs and LOAELs for the RfC, in Table 4-3, row 2 of the draft assessment,
14 the 30 ppm LOAEL is given as the mean time-weighted average exposure for the workers
15 in the Chia et al. (1997) and Goh et al. (1998) study and the mean exposure duration is
16 stated to be 5 years. The 30-ppm figure was obtained by personal breathing zone
17 monitoring on 12 of 85 individuals who participated in the study. There is no indication
18 given in the articles as to whether it is reasonable to assume that exposure levels in the
19 factory had not changed significantly over the past 5 years. This would be important to
20 know to assess whether it is appropriate to use the 30-ppm level as the mean chronic
21 exposure level. The articles also do not mention whether the workers had any other
22 concomitant exposures. It is also not clear why the authors chose to use analysis of
23 variance, with years of TCE exposure as a categorical variable, rather than linear
24 regression, with years of TCE exposure as a continuous variable, as the method of
25 analysis. In fact, the categories into which TCE exposure duration is grouped are
26 different in the two papers even though the data are the same. Another shortcoming is the
27 absence of an unexposed control group. Despite these shortcomings, the authors did find
28 significant relationships between some serum hormone concentrations and years of
29 exposure to TCE using analysis of covariance with adjustment for age, smoking, and
30 testicular size. There were significant inverse relationships between TCE duration and
31 serum FSH, sex hormone binding globulin, and insulin levels. There was a significant
32 positive relationship between dehydroepiandrosterone (DHEAS) levels and TCE
33 duration. There was also a significant negative correlation between years of TCE
34 exposure and testosterone levels, but this relationship became non-significant after
35 adjustment for age, smoking, and testis size. The argument can be made that the authors
36 should not have adjusted for age or testes size because neither one meets the criteria for a
37 potential confounding variable of being significantly associated with the exposure
38 variable and the outcome variable. Age clearly is a surrogate for years of TCE exposure
39 in that older workers are likely to have more years of exposure. Although testosterone
40 levels tend to decrease with age, this is typically not observed until after the age of 50. In
41 this young cohort it is very unlikely that the significant negative correlation observed
42 between age and testosterone levels represents the effect of age on testosterone. It is more
43 likely that age is acting as a surrogate for exposure and, thus, that adjusting for age will
44 falsely reduce the relationship of interest (i.e., the relationship between exposure and
45 testosterone). For testes size, there is no reason to believe that this variable would be

1 independently associated with exposure, and therefore, it does not make sense to adjust
2 for it.

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

14
15 Although the LOAELs for the human neurotoxicity and endocrine toxicity studies
16 have a good bit of uncertainty associated with them, as illustrated by the above
17 discussions, the estimated HED LOAELs from 5 different human studies fall within a
18 remarkably narrow range (7-16 ppm). Additional confidence in using these levels as the
19 point of departure is provided by the subchronic rat neurotoxicity study by Arito et al.
20 (1994) from which a HED LOAEL of 9 ppm was derived, and the LOAEL of 12 ppm for
21 liver toxicity in the subchronic mouse study by Kjellstrand et al. (1983). It may be more
22 appropriate to use the animal studies and perhaps the Ruitjen et al. (1990) study as the
23 critical studies, with the other human studies as supportive studies. This is mainly
24 because none of the human studies had long-term exposure data on the individual level.
25 The study by Ruitjen et al. (1990) had the best exposure information (area samples from
26 the plant spanning several decades and specific information about when changes such as
27 installation of exhaust ventilation occurred) and chronic exposure indices based on the
28 monitoring data were calculated for each subject. The Vandervort and Pelakoff (1973)
29 and Okawa and Bodner (1973) studies were National Institute for Occupational Safety
30 and Health (NIOSH) Health Hazard Evaluations that had good current exposure data in
31 the form of personal air samples and urinary TCA. Both studies lacked information about
32 chronic exposure conditions, and the Okawa study lacked a control group or any analysis
33 of an exposure effect relationship.

34
35 In regard to the Agency's choice of NOAELs and LOAELs for the RfD, the Panel
36 was not in agreement on whether an uncertainty factor for a LOAEL is needed, given that
37 the LW/BW is considered more of an early event in the toxicity process and a sensitive
38 indicator of potential liver effects observed at later times. The sizes of the changes are
39 small (12 % -7%) (see Barton and Clewell, 2000). Other panelists supported the use of a
40 ten-fold uncertainty factor for LOAEL to NOAEL. Several panelists questioned why
41 EPA uses a full ten-fold safety factor in the derivation of the RfC, but decreases the
42 factor to only three-fold for the RfD. The Panel suggests that EPA clarify this issue in the
43 draft assessment.

44
45 Another view cautioned EPA in treating the LED10 as a LOAEL. The original
46 basis for the selection of LED10 is that it most closely estimated NOAELs for large

1 numbers of developmental studies (Allen, 1994). Other panelists argued that the LED10
2 is by definition an effect level and that therefore it more closely approximates a LOAEL.
3 The benchmark dose approach is considered a more preferred approach to estimate the
4 point of departure that takes into account the experimental variability. Therefore it
5 should be reducing uncertainty, not requiring more uncertainty to be added.

6
7 In regard to the Agency's choice of NOAELs and LOAELs for the RfC, Barton
8 and Clewell argued that the LOAEL of the Arito et al. (1994) study reflected a minimal,
9 though statistically significant effect, and should be evaluated to determine if clinically
10 significant effects were seen at the lowest dose level. Therefore, the application of a 10-
11 fold uncertainty factor for LOAEL to NOAEL extrapolation is justified if effects are
12 noted in the Arito et al. neurotoxicity study and are consistent with the weight of
13 evidence from other carefully conducted neurotoxicity studies. The Kjellstrand et al.
14 (1983) study also identified a LOAEL (for liver weight), and the application of an
15 additional factor may be justified depending on the duration-response trends for this
16 endpoint. On the other hand, some panelists suggest that if the benchmark dose (derived
17 by Barton and Clewell) is used, then an uncertainty factor should not be automatically
18 applied. There is a question in the minds of some panelists about why only a three-fold
19 uncertainty factor is used for the LOAEL to NOAEL extrapolation in the derivation of
20 the RfD, when a ten-fold factor is used here. They suggested that the Agency improve
21 the consistency of the draft assessment by applying a standard ten-fold factor throughout.

22 23 2.5. Other Factors

24
25 Some panelists believed that use of medications and presence of diseases is part
26 of the default human variability factors and should not be double counted, while others
27 pointed out that these might further extend the range of variability and would require an
28 additional uncertainty factor Clewell makes a point in his public comments submitted to
29 the Agency that should be considered as well, namely, that induction of CYP2E1 is not
30 likely to have a major impact on increasing oxidative metabolism at environmentally
31 relevant concentrations of TCE. This argument may or may not be correct and would be a
32 good topic for future research.