Peer Review Workshop
for EPA's IRIS Toxicological Review of
1,1,2,2-Tetrachloroethane
Human Health Assessment

Reviewer Post-Meeting Comments

February 23, 2010

Notice

Pre-meeting comments were prepared by each consultant individually prior to the meeting. They are preliminary comments only, and are used to help consultants become familiar with the document and charge questions, develop the agenda, and identify key issues for discussion. During the meeting, consultants may expand on or change opinions expressed in their pre-meeting remarks and may introduce additional issues. For these reasons, pre-meeting comments should be regarded as preliminary and do not reflect the final conclusions and recommendations of individual consultants. After the meeting, reviewers will prepare post-meeting comments that will reflect their final views. Post-meeting comments will be provided in the workshop report.

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Biographies

Bruce C. Allen

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Mr. Allen received a Bachelor of Arts degree in Philosophy and a Bachelor of Sciences degree in Mathematics from the University of Washington, and his Masters degree in Biomathematics from North Carolina State University in 1980.

His work experience includes:

- Site manger for a clinical trial for the Department of Biostatistics, University of North Carolina.
- Risk Assessor for K.S. Crump and Company, Clement International, ICF Consulting, Environ International, and, currently, as an independent consultant.

His areas of expertise include:

- Statistical analysis, including computer-intensive approaches such as bootstrap, Monte Carlo and Bayesian MCMC techniques
- Dose-response analysis and software development
- Benchmark dose modeling and methods development
- Uncertainty analysis

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Dr. Bruckner is a professor of pharmacology and toxicology at the University of Georgia. His research includes validation of PBPK models to assist in predicting administered dose/exposure levels anticipated to produce effects in humans, including children. He has served on numerous state and national panels, including the National Academy of Sciences' Board on Environmental Studies and Toxicology and the Life Sciences Institute's Working Group on Physiological Parameters for Children. He has published in numerous professional journals, including the Journal of Toxicology and Environmental Health, Toxicology and Applied Pharmacology, and Toxicological Review.

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Dr. Dekant received a Dipl. Chem in Chemistry in 1980 and a Dr. Rer. Nat. in toxicology in 1984, both from the University of Würzburg, Germany. He is currently a professor in the Department of Toxicology at the University of Würzburg. He is a member of professional societies including the Society of Toxicology, International Society for the Study of Xenobiotics, and Deutsche Gesellschaft für Pharmakologie und Toxikologie. Dr. Dekant has conducted research in carcinogenicity, metabolism, nephrotoxicity and pharmacokinetics. He has authored or co-authored over 150 peer-reviewed articles in such scientific journals as *Toxicology*, *Toxicology and Applied Pharmacology*, and *Toxicological Science*, to name a few. He is the Editor for *Toxicology Letters*, and is currently a member of the editorial boards for *Xenobiotica*, *Toxicological Sciences*, *Reviews in Toxicology*, and *Toxicology and Applied Pharmacology*.

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Dr. Hattis is a professor in the Center for Technology, Environment, and Development at Clark University. His research focuses on methodologies for quantitative health risk assessment for cancer and non-cancer health effects, human variability in susceptibility to toxic effects, and pharmacokinetic and Monte Carlo simulation modeling. He has served on numerous committees, including the U.S. EPA Science Advisory Board's Environmental Health Committee, the National Research Council's Committee on Neurotoxicology and Models for Assessing Risk, and the National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction. His work includes numerous publications in professional journals and books such as Toxicokinetics in Risk Assessment, Risk Policy Report, and Environmental Health Perspectives.

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Dr. Kacew is currently Associate Director of Toxicology, McLaughlin Centre for Population Health Risk Assessment at the University of Ottawa, where he is also a Professor of Pharmacology, and Scientist at the University's Institute for Population Health. Dr. Kacew is the Colgate-Palmolive Visiting Professor at the University of New Mexico, and holds Visiting Professorships at the University of Guildford in Surrey, England, the Institute of Toxicology at National Taiwan University in Taipei, Taiwan, the Joszef Fodor National Center of Public Health in Budapest, Hungary; the Department of Occupational Health, Shanghai Medical University in Shanghai, China; at Zhehjiang University in Hangzhou, China; at Nanjing Medical University, Nanjing, China; and the Division of Toxicology at Sung Kyun Kwan University in Suwan City, Korea.

Dr. Kacew is currently the Editor-in-Chief of the *Journal of Toxicology and Environmental Health, Part A, Current Issue*; and the *Journal of Toxicology and Environmental Health, Part B, Critical Reviews*. He is the North American Editor for *Toxicology and Environmental Chemistry*; Associate Editor of *Toxicology and Applied Pharmacology*; Associate Editor of *The Scientific World Journal* (TSW Toxicology); Editor of the Encyclopedia of Environmental Health, and Lu's Basic Toxicology 4th and 5th Editions, and Guest Editor of a special issue of *Toxicology and Applied Pharmacology* entitled "Toxicological Reviews in Fetal Childhood Development."

Dr. Kacew is a member of the Board of Trustees of Toxicology Excellence in Risk Assessment (TERA). For the National Academies of Science (NAS) is was formerly a member of the Committee on Toxicology, served as Chairman on the NAS Subcommittee on Iodotrifluoromethane and Chairman on the NAS Subcommittee on Tetrachloroethylene. He was a member of the NAS Subcommittees including flame retardants, jet propulsion fuel-8, and Toxicologic and Radiologic Effects from Exposure to Depleted Uranium During and After Combat. For the U.S. EPA, he served as Chairman of an Expert Peer Review Panel for the Provisional Toxicity Values for Total Petroleum Hydrocarbons, member of a Panel on the Beryllium Lymphocyte Proliferation Screening Test, an Expert Panel Member on the Breast Milk Monitoring for Environmental Chemicals in the U.S., and as part of a U.S. EPA initiative, was a Core Panel Member of the Voluntary Children's Chemical Evaluation Program (VCCEP). For Canada, a member of the Advisory Expert Committee of the Canadian Network of Toxicology Centres, an Expert Panel Member on the Pest Management Regulatory Agency of Health Canada on Citronella Science review; and Expert Panel Member of the Council of Canadian Academies on Integrated Testing of Pesticides.

Dr. Kacew has been a peer reviewer for the EPA's Integrated Risk Information System (IRIS) documents, the EPA's Health Effects Assessment Summary Table (HEAST) Chemicals, chemical-specific issue papers for the EPA's Superfund Technical Support Center, and has served on the National Institutes of Health (NIH) grant study sections. Dr. Kacew received the Achievement Award of the Society of Toxicology of Canada in 1983, the Achievement Award of the Society of Toxicology in 1986, the ICI (Zeneca) Traveling Lectureship Award in 1991, the US-China Foundation Award in 1995, the Colgate-Palmolive Visiting Professorship Award in 1997, and the Public Communications Award of the Society of Toxicology in 2002. He is author of over 150 papers, reviews and book chapters with emphasis in general toxicology, including renal, hepatic, and pulmonary toxicology. He has edited several texts on pediatric toxicology and serves on several editorial boards.

Responses to General Charge Questions

(A) General Charge Questions

A-1. Is the Toxicological Review logical, clear and concise? Has EPA clearly synthesized the scientific evidence for noncancer and cancer hazard?

Allen

In general I found the review to be logical. I am of the opinion that clarity (and perhaps conciseness) could be improved by two modifications to the style of the document. First, use more subheadings to help identify when the subject under consideration has changed. Primarily, this would just entail having subheadings to identify the study being discussed, particularly in Section 4. The more significant suggested change would be to forego the narrative style of exposition and go more with a fairly uniform, consistent, and easily reader-recognizable set of bullet items. So, for example in Section 4 where all the studies are being introduced, just provide a list of the following items (and perhaps others as needed), in the same order, for each study:

- Study authors
- Date
- Species/strain/sex
- Exposure scenario
- Endpoints examined
- Significant effects found, by dose level
- Notes and other important considerations (which could be more narrative)

I liked the summary tables (e.g., 4-18) and thought that much of the narrative could have been totally eliminated in favor of summaries like that and the suggested bulleted itemization of key features in the text.

Much of the text in Section 5 merely rehashes the same information that is presented in Section 4. The subheadings such as "5.1.1.1. Choice of Principal Studies and Critical Effect – with Rationale and Justification" [emphasis added] should focus on the rationales and justifications rather than have so much reiteration of the study findings, which could be cited from where they are given in Section 4, especially if additional subheadings and bulleting of salient features were added there.

Bruckner

This Toxicological Review is clean, concise and usually quite logical. It is generally well written, though some suggested editorial changes have been made in the text in red ink. Parts of the Toxicokinetics section are naively written, so a number of changes and additions are recommended, as specified under my Specific Comments. The document's authors have done a good job synthesizing/summarizing data from studies of non-cancer effects. A somewhat more inclusive and balanced perspective on carcinogenicity potential should be provided.

Dekant

In general, the review is logically structured. However, it would benefit from some condensation since summaries and discussion points are repeated. The scientific evidence is acceptably synthesized in most parts of the document.

Hattis	Yes, this more or less a standard IRIS analysis. As mentioned by Dr. Allen, some greater use of tables rather than narrative summaries of individual studies might be helpful.
Kacew	In general, the overall organization and scientific soundness of the issue paper is appropriate and clearly presented, there are several sections that need to be revised and these are outlined below. There are certain general comments that need to be addressed in order to provide a more succinct, scientific report. The correct and appropriate term for humans, rats and mice is gender or genders and NOT sex or sexes which appear throughout the text. Further when describing ALT, AST, SDH, GST, etc .one is measuring an activity, which needs to be inserted into the text, and NOT a level or content. In the case of cholesterol, glucose, protein, Hb, etc one is measuring levels and this need to be inserted into the text. Page by page comments for editing and clarification are as follows: 1) On page 5 line 21 change to "microsomal" and specify is this hepatic, renal or?? 2) On page 6 line 16 what does "considerable" mean. If the change is significant then this is the case. Is this 80%, 50%, etc?? Delete term considerable which has no biological meaning. 3) On page 6 line 36 what does "high" mean. Is this 80%, 90% ?? Delete term "high" and state amount. 4) Page 7 line 1 What does "High levels" mean and insert "radioactivity" 5) Page 7 line 2 it is "adrenal cortices and interstium of testes" (2 adrenals and 2 testes) 6) Page 8 line 18 is it "Mean levels…"? 7) Page 8 line 22 insert "..simultaneous ip injection…" 8) Page 8 line 37 change to "…reported to produce.." 9) Page 9 lines 10, 14, change sexes to "…genders.." 10) Page 9 line 28 insert "…testes.." 11) Page 11 line 29 insert "..kidneys" 12) Page 13 line 35 change to "..10 minutes produced.." 13) Page 14 line 3 the term "slight" has no biological, meaning. Was the change significant, then state. If not then delete. 14) Page 14 line 2 What does "a slight but progressive anemia mean? Was there anemia or not? 15) Page 14 line 9 change to "….mixed-gender" 16) Page 16 lines 12, 18, & 34; Page 18 lines 4 & 12; Page 19 line 3; Page 20 lines 2 & 18 change to gender 17) Page 19 insert "..increases in ALT activity and SDH activity..'

18) Page 20 line 2 insert "..increases in ALT activity.."

19) Page 20 lines 3-4 for cholesterol and bile acids insert "..levels"

20) Page 20 line 6 for 5'nucleotidase insert "..activity"

21) The summary of the description of the NTP (2004) study on page 21 is NOT precise. On page 21 line 9 it should state that increases in relative liver wt. at 40 mg/kg were in males and females. Similarly at 80 mg/kg there was hepatocellular hypertophy and spleen pigmentation in males and females. However increases in serum ALT and SDH activity occurred in MALES at 80 mg/kg but at 170 mg/kg in FEMALES. Serum cholesterol levels were decreased in FEMALES at 80mg/kg but at 320 mg/kg in MALES. The text on page 21 states that cholesterol was increased BUT it was actually DECREASED. Following ALP the term "activity " is missing on page 22 line 2 while bile acids needs "levels" on page 22 line 2.

22) Page 22 lines 11, 13 & 21; Page 23 line 8 change to gender

23) Page 22 line what is "Thinness"???

24) Page 22 line 32 see comment 13 regarding use of term " slightly" and delete

25) Page 25 line 8 the phrase "SDH levels" is NOT correct the levels were NOT measured. It was the activity. Further insert that it was "serum"

26) Page 25 lines 2-18 you need to insert "activity" after the enzymes and "levels" after protein, albumin, cholesterol, etc.

27) Page 26 line 11 states that based upon the data that a NOAEL of 80 mg/kg was identified. However in females at 80 mg/kg there was a significant increase in absolute and relative liver wt. as well as an increase in SDH activity and hepatocyte hypertrophy. In essence there were effects and thus this can NOT be a NOAEL.

28) Page 27 lines 6 & 7; Page 28 line 7; Page 30 lines 7& 12 change to gender

29) Page 30 line 23 was the "very slight decrease" significant? This phrase has no biological meaning and hence delete if NOT significant.

30) Page 31 line 1-6 the Table describing the renal changes is MISSING but tables are provided for mammary gland, pituitary (Table 4-10 & 4-11) for liver (Table 4-12) and for lung (Table 4-13). This is odd and disturbing as on Page 32 lines 5-7 the LOAEL and NOAEL are based upon the kidney data and these are the data NOT provided in a Table. As there seems to be no data provided for a dose lower than 142 it is not clear that dose is a NOAEL as there was chronic inflammation in males and hence this can not be a NOAEL. Clearly a Table is required for kidney data.

31) On page 31 line 7 for consistency delete the actual p value from the text. The text would need to provide ALL values for all studies which is not feasible and unwieldy. Hence delete the p actual value from the text and simply state significant which is sufficient.

32) On page 31 line 17 change sexes to " ….genders….."

33) Page 32 line 24 the phrase "..a slight decrease.." has no biological meaning; hence delete (See point 29).

34) Page 33 line 22& 31; Page 34 line 1 "kidneys"

35) Page 33 line 22 "testes"

36) Page 33 line 35 "Serum phosphatase activity levels.."

37) Page 34 line 16 "..acetylcholine levels…"

38) Page 35 line 19 what is "slightly rough fur..???

39) Page 35 line 26 "Small but statistically significant.." What is the implication of this statement? If data are significant, then that is the case. There are NO degrees of significance.

40) Page 35 line 31 change to "..produced a statistically..

41) Page 37 line 2 "genders"

42) Page 38 line 19 delete actual p value from text (See point 31)

43) Page 38 line 20 the serum levels of AST & ALT were NOT measured. Serum AST and ALT activity levels were measured; hence change.

44) Page 38 line 22 insert "serum" prior to ALT and on line 23 prior to ALT

45) Page 38 line 24 insert " hepatic microsomal G6Pase.."

46) Page 39 Table 4-14 Title is NOT correct. Serum AST and ALT are NOT effects on liver. These enzymes are merely indicators of liver function. The other parameters were actually measured in liver.

47) Page 39 line 5 insert " ..aminopeptidase activity..

48) Page 39 line 8; Page 42 line 3 & 5 insert "..ALT activity.." or "..AST activity

49) On page 40 line 12; Page 42 line 5 term "slight" has no biological meaning and needs to be deleted

50) On page 40 line 17; Page 54 line 5; Page 60 line 1; Page 61 line 16

change caused to " …produced…."

51) Page 42 line 23 "Increased hepatic glycogen content.."

52) Page 43 line 2; page 54 line 14 delete actual p value from text (See point 31)

53) Page 43 line 13; Page 44 line 4 & 23; Page 45 line 28 " kidneys"

54) Page 44 line 24; Page 45 line 24, 31, 33 & 35; Page 46 line 3; Page 47 line 14, 19 & 21

change sex or sexes to "gender or genders"

55) Page 45 line 34; Page 46 line 38 what does "thin" mean?

56) Page 53 line 6 change to doses to "Higher concentrations…" as this is in vitro

57) Page 54 Table 4-16 DELETE p values from Table as ALL other Tables do NOT present p values.

58) The summary text on page 56 lines 4-7 is imprecise and NOT accurate. AST and ALT activities increases were NOT measured in "hepatic" as clearly shown in the Table. These enzymes indicative of liver function were measured in "serum". Further insert "decrease in hepatic microsomal G6Pase" Line 6 for precision should read "ascorbic acid levels " "serum aminopeptidase activity" and line 7 "ALT activity"

59) Page 57 in the actual Table 4-18 for Cottalasso it needs to insert "activity" following ALT and AST; while "levels needs to be inserted following triglycerides and dolichol

for Schmidt insert ascorbic acid levels and aminopeptidase activity

This also applies to the NTP 2004 study on page 58 insert "activity" for enzymes and "levels" for constituents

60) Page 60 lines 18 -30 are again imprecise. It clearly states that at 20 mg/kg-day hepatocellular cytoplasmic vacuolization was noted in male rats. However, on line 25 it states the NOAEL is 20mg/kg-day. If there is an effect recorded at this dose then this constitutes a LOAEL and NOT a NOAEL. Further following SDH or ALP insert "activity" and following cholesterol or bile acids insert "levels". Further with respect to the NCI study a TWA of 43 mg/kg-day how did tetrachloroethane reduce mortality?? Does this infer that tetrachloroethane increases survival?

As an effect was noted at 43 mg/kg-day then on line 29 the 62 mg/kg-day can NOT be a NOAEL as an effect was found at 43 mg/kg-day in females.

61) Page 60 lines 35-37 insert "activity" following enzymes and "levels" following constituents for precision.

62) Page 61 lines 4-5 the NCI 1978 study did NOT record increases in the renal parameters; what was reported but was actually "..increases in frequency or number of animals with hydronephrosis…."

63) Page 65 Table 4-20 for Deguchi 1970 what does "slight" mean??

64) Page 68 line 2; Page 70 line 29; Page 74 line 24 change cause to "produce"

65) Page 68 line 22 & 33; page 73 line7 "kidneys'

66) Page 68 line 30 "ascorbic acid levels"

67) Page 68 line 34 what is "light congestion"??

68) Page 70 lines 6, 7 & 25; page 72 line 8; Page 73 line 30 & 34; Page 74 lines 28, 29 &32

change sexes to "genders"

A-2. Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of 1,1,2,2-tetrachloroethane.

Allen	I know of no additional studies that should be considered.
Bruckner	No additional toxicity or carcinogenicity studies were located that should be considered in deriving a RfD, RfC or cancer slope factor. A number of additional papers that provide additional insight, or perspective on pertinent issues have been cited and referenced at the end of my comments.
Dekant	None found in MedLine.
Hattis	Detection of in vitro clastogens and spindle poisons by the mouse lymphoma assay using the microwell method: interim report of an international collaborative study. Re-evaluation of chromosomal aberration induction on nine mouse lymphoma assay "unique positive' NTP carcinogens. Matsuoka A, Yamakage K, Kusakabe H, Wakuri S, Asakura M, Noguchi T, Sugiyama T, Shimada H, Nakayama S, Kasahara Y, Takahashi Y, Miura KF, Hatanaka M, Ishidate M Jr, Morita T, Watanabe K, Hara M, Odawara K, Tanaka N, Hayashi M, Sofuni T. Mutat Res. 1996 Aug 12;369(3-4):243-52. Division of Genetics and Mutagenesis, National Institute of Health Sciences, Tokyo, Japan. matsuoka@nihs.go.jp In a collaborative study organized under the JEMS MMS, nine mouse lymphoma assay (MLA) "unique positive' NTP rodent carcinogens were re-evaluated by an in vitro chromosomal aberration assay using Chinese hamster lung fibroblast cells (CHL/IU). Six of nine chemicals induced chromosomal aberrations; bromodichloromethane, chlorendic acid and isophorone induced structural aberrations, and chlorodibromomethane, pentachloroethane and 1,1,1,2-tetrachloroethane induced numerical aberrations (polyploidy). These six chemicals, therefore, are not uniquely positive in the MLA. The difference between the NTP results and ours might be due to the use of different cell lines and protocols, and in some cases, to different interpretations of polyploidy. The remaining three chemicals, benzyl acetate, cinnamyl anthranilate and trichloroethylene, were negative in this study. Sofuni T, Honma M, Hayashi M, Shimada H, Tanaka N, Wakuri S, Awogi T, Yamamoto KI, Nishi Y, Nakadate M. Mutagenesis. 1996 Jul;11(4):349-55. National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158, Japan. Under the auspices of the Ministry of Health and Welfare of Japan and the Japanese Pharmaceutical Manufacturer Association, a collaborative study of the mouse lymphoma assay (MLA) was conducted by 42 Japanese laboratories and seven overseas laboratories to clarify the performance of the MLA for the detection of in vitro clastogens and spindle poisons. Twenty-one chemicals that were positive in in vitro chromosomal aberration assays (CA) but negative in

	bacterial reverse mutation assays (BRM) were examined by the MLA using the microwell method. All chemicals were coded, and each chemical was tested by two or three laboratories. Positive responses were obtained with 14 chemicals: mitomycin C (an internal positive control), arsenic trioxide, cadmium sulphate, chlorendic acid, cytosine arabinoside, diethylstilbestrol, eugenol, 5-fluorouracil, griseofulvin, hexamethyl phosphoramide, hydroxyurea, methotrexate, monocrotaline and pentachloroethane. Two chemicals (benzene and chlorodibromomethane) showed positive responses in one of two laboratories and were judged probably positive chemicals. Three chemicals (bromodichloromethane, isophorone and tetrachloroethane) were inconclusive because of a marginal response in one laboratory and a negative response in the other. Urethane was judged probably negative because two laboratories out of three showed clear negative responses. Dideoxycytidine (DDC) was a clear negative chemical in this study. The present results showed that 75.0% of the test chemicals (15/20, excluding mitomycin C) were positive, 15.0% (3/20) were inconclusive, and 10.0% (2/20) were negative. This suggests that the MLA may detect a majority of CA-positive chemicals. The inconclusive chemicals, however, are critical for the judgement of the MLA potential to detect clastogens. The findings that DDC was clearly negative suggests that the MLA may not be able to detect some clastogens. To clarify these issues, we began the second phase of the collaborative study with other BRM-negative and CA-positive chemicals. Blood concentrations of volatile organic compounds in a nonoccupationally exposed US population and in groups with suspected exposure. Ashley DL, Bonin MA, Cardinali FL, McCraw JM, Wooten JV. Clin Chem. 1994 Jul;40(7 Pt 2):1401-4. Division of Environmental Health Laboratory Sciences, Centers for Disease Control and Prevention, Atlanta, GA 30341-3724. Exposure to certain volatile organic compounds (VOCs) commonly occurs in industrialized countries. We developed a method for measuring 32 VOCs in 10 mL of whole blood at low concentration. We used this method to determine the internal dose of these compounds in 600 or more people in the US who participated in the Third National Health and Nutrition Examination Survey. From our study results, we established a reference range for these VOCs in the general population of the US. We found detectable concentrations of 1,1,1-trichloroethane, 1,4-dichlorobenzene, 2-butanone, acetone, benzene, chloroform, ethylbenzene, m,p-xylene, styrene, tetrachloroethane, and toluene in most of the blood samples of nonoccupationally exposed persons. The accuracy of VOC evaluations depends on the ability of investigators to make sensitive and reproducible measurements of low concentrations of VOCs and to eliminate all sources of interference and contamination. Paper on findings probably worthy of mention to establish some specific frequency of detection over background—go to original data.
Kacew	I am not aware of any additional studies with 1,1,2,2-tetrachoroethane.

Responses to Chemical-Specific Charge Questions

(B) Oral reference dose (RfD) for 1,1,2,2-tetrachloroethane

B-1. Subchronic and chronic RfDs for 1,1,2,2-tetrachloroethane have been derived from a 13-week oral gavage study (NTP, 2004) in rats and mice. Please comment on whether the selection of this study as the principal study has been scientifically justified. Please identify and provide the rationale for any other studies that should be selected as the principal study.

Allen	I am satisfied with the choice of this study for both the subchronic and chronic RfD derivations. It appears to be the best study among the subchronic studies and it looked for effects in what appears to be the most sensitive organ (liver). The use of the NTP (2004) study for the chronic RfD may be open to more concern, given that there was the NCI (1978) chronic study, but I was convinced by the arguments in favor of using the subchronic study with an additional uncertainty factor. I found the NCI (1978) study to be problematic for several reasons and would not want to rely on that study for a chronic RfD. Nevertheless, I wonder if there could be more justification added to that given on pp. 81-82, especially with respect to the statement that high incidences of hepatocellular tumor in all groups preclude evaluation of noncancer effects in the liver. Why is that so?
Bruckner	The subchronic oral feeding study by NTP (2004) is clearly the best choice for the principal study. This recent, well-conducted and reported investigation involved assessment of effects of five doses of TET on a wide variety of toxicity indices and tissues of both sexes of mice and rats. A major attribute of the study was the oral dosage regimen. Administration of the chemical in the animals' feed is much more representative of actual human exposures than gavage dosing.
Dekant	Since the database on 1,1,2,2-tetrachloroethane is limited and only few useful studies are available, the study is appropriate to derive a RfD. The study is of good quality, used a wide dose range and measured a variety of endpoints.
Hattis	The only other study that seems to be a candidate is the small reproductive study of Gulati which found reductions in fetal body weight. However this study is very small—involving only 8 or 9 litters per dose group. Although it provides what may be a more significant endpoint for human health protection I think EPA has chosen reasonably in going with NTP study and relative liver weight as the critical study and endpoint.
Kacew	The inability to use human data to derive an oral subchronic and chronic RfD for 1,1,2,2-tetrachloroethane is justifiable. The use of the NTP (2004) study based upon treatment with 6 doses in 2 species for 13 weeks is a comprehensive well-designed study. This clearly is the most suitable study for derivation of the oral subchronic and chronic RfD. This study provides far more sensitive data than the other studies for derivation of the oral RfD. Although there is a chronic NCI (1978) study available the high incidence of endemic chronic murine pneumonia raises doubts as to whether the chemical or simply the compromised health of the animal contributed to the adverse effects. The fact that a NOAEL and LOAEL in the NCI (1978) study along with high incidences of hepatocellular tumors also justifies the non-use of this study. Hence the use of the NTP (2004) is preferred to derive the oral chronic RfD. It should be borne in mind that the text pages 76-78 lacks scientific precision as follows:

1) Page 76 line 19 & 20; Page 77 line 9; page 78 lines11& 31

change sex or sexes to gender or genders

2) Page 76 line 27 enzyme activity levels

3) Page 76 line 28 ALT and SDH activity

4) Page 76 line 29 cholesterol levels

5) Page 76 line 29 ALP activity

6) Page 77 line 3 ALT, ALP activity, bile acid levels

7) Page 77 line 4 hepatic 5'-nucleosidase activity

8) Page 77 line 5 SDH activity

9) Page 77 line 21 testes

10) Page 77 line 28 phrase " Small but statistically significant.." has NO biological relevance as it was significant!

11) Page 78 line 18& 24 it is ALT, ALP and SDH activity levels

B-2. Increased relative liver weight was selected as the critical effect for the derivation of the subchronic and chronic RfDs. Please comment on whether the rationale for the selection of this critical effect has been scientifically justified. Please provide a detailed explanation. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

Allen

I believe relative weight is more appropriate than absolute weight in this case where body weights in general are being affected. I perceive that as a "normalization" that "corrects" for effects on the total body weight (the reduction of which may reflect other adverse effects that are occurring) so that the effect on the liver, per se, can be highlighted. The only question I had about the rationale for picking relative liver weight as the critical endpoint (over other possible choices such as the enzyme changes) was the statement (p. 78, lines 27-28) that it occurs early in the process leading to hepatocellular necrosis. Would not increases in liver weight reflect other, earlier changes that have been going on long enough to cause the cell proliferation, inflammation, or whatever other effects are responsible for liver weight gain? If the thinking is that the other available metrics reported in the NTP study do not represent any of those earlier processes, then that should be stated explicitly as a rationale for picking the more generic relative liver weight endpoint.

I believe the selection of the endpoint (from among those considered to be clinically relevant) that results in the most conservative (health-protective) POD to be satisfactory. Thus the choice of relative liver weight (as opposed to enzyme changes, bile acids, or the developmental toxicity endpoint) is justified.

I particularly like Figure 5-1, since it gives an idea of the range of doses available for each endpoint (which would be even more informative and important if there had been more studies under consideration), though I would suggest these changes to make it even more informative and useful:

- in place of (or in addition to) the bar representing the range of doses for each endpoint, include symbols for all the doses, not just the NOAEL and LOAEL, because the absolute number of dose groups and their spacing is important information
- include the BMDL (and perhaps the BMD) that was derived as a potential POD for each endpoint, because it is good to see where the POD candidates are in relation to the experimental doses and it gives a visual representation of the information about the differences in potential PODs (information that is given in tabular form in Table 5-3)

Bruckner

Selection of increased relative liver weight as the critical effect for RfD determination has been justified satisfactorily. Increased relative liver weight, however, is a less toxicologically significant index of liver change than increased absolute liver weight, due to the treatment-induced loss of body weight. Decreased body weight alone can result in increased relative liver weight, without any effect on actual liver weight. Alternatively, the document's authors could have chosen increased serum enzyme activity, a true measure of hepatocellular damage, as their basis for deriving RfDs. The NOAEL and LOAEL for this truly adverse effect in male rats were 40 and 80 mg/kg, rather than 20 and 40 mg/kg for increased relative liver weight. One should choose the most sensitive toxicologically-significant endpoint rather than merely the most sensitive endpoint. It might be argued that increased relative liver weight is an early effect on a continuum with hepatocellular necrosis, but there was no scientific evidence to support this supposition for TET or related short-chain halogenated aliphatic hydrocarbons (halocarbons).

Dekant

The selection of this endpoint is well justified and is more appropriate to use for RfD-derivation as compared to hepatocellular vacuolization. EPA rationally describes the selection criteria.

Hattis

The only other endpoint that seems to be a candidate is the finding of reduced fetal body weight in the small reproductive study of Gulati in rats. Although it provides what may be a more significant endpoint for

human health protection, and I think the benchmark risk level should be much lower than the 5% used for this endpoint (see supplementary comments below) I think EPA has chosen reasonably in going with NTP study and relative liver weight as the critical study and endpoint because of the weaknesses of the Gulati study

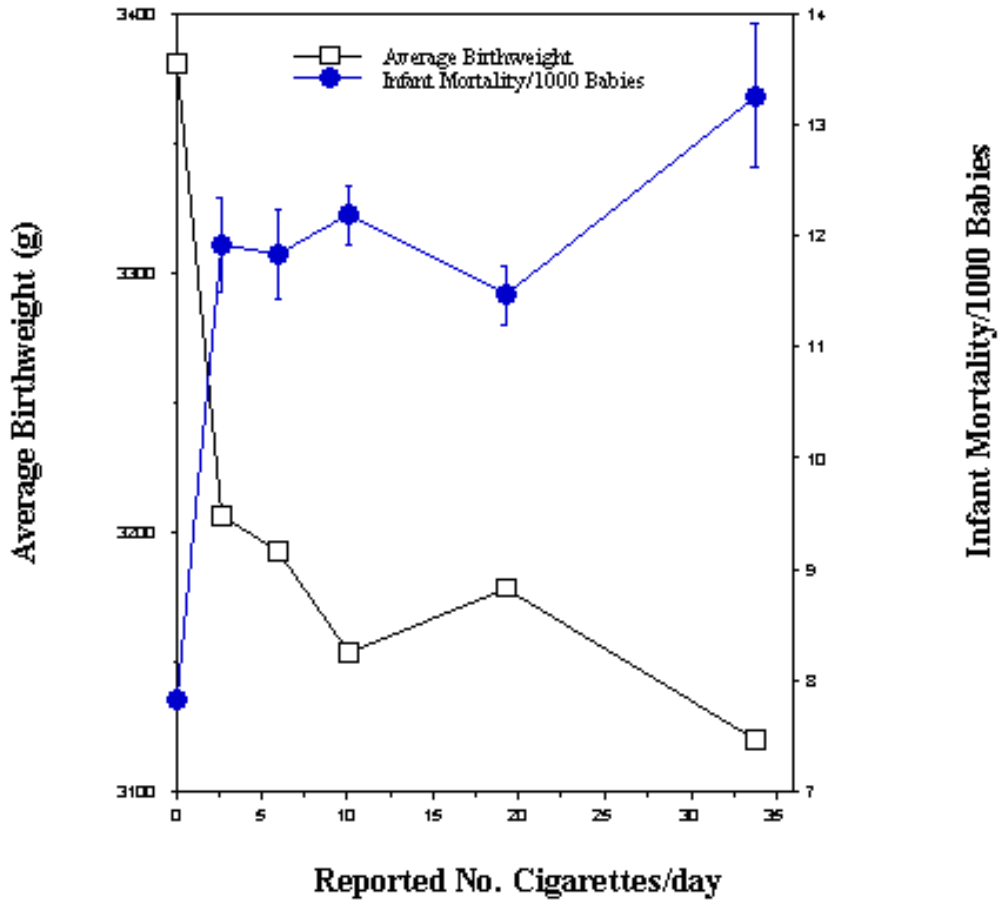
Supplementary comments:

- I think the best I can do to provide guidance on an appropriate benchmark response level for fetal growth restriction is to look to the analogous degree of fetal growth restriction and infant mortality associated with cigarette smoking, and the fetal growth restriction seen with criteria air pollutants such as particulates. Both of these are covered in the air toxics paper

Hattis, D. and Keaney Lynch, M. "Alternatives to Pollutant-by-Pollutant Dose-Reponse Estimations for Air Toxics" EP-W-05-022 WA 3-80 Task 2 White Paper, 2009.

--start with Figure 1 for cigarette smoking. A pack per day of personal smoking makes a difference of about 200 g in average birth weight. With a standard deviation of about 500 g, this represents about 0.4 standard deviations. You can see from the figure that this is associated with about a 4/1000 increase in infant mortality, from 8/1000 to the neighborhood of 12/1000. These calculations were based on older data (probably from the 1980s) when infant mortality rates were larger than they are now. However if there is an appreciable possibility that these responses are connected, I think it is crazy to consider as much as a 1 standard deviation change in fetal weight to be the practical equivalent of a NOAEL for regulatory purposes. I think public policy must aim to keep the magnitude of effect much lower than that. On this scale, a 1% change in birth weight--about 35 grams in people, or 0.07 standard deviations, is I think the largest amount that should potentially be considered as representing a LOAEL, and even that I can only recommend with some reservations. A 35 gram difference in people is a magnitude of change that can be detected epidemiologically. See for example the estimates of the magnitude of effect seen for several of the criteria air pollutants (Tables 4-1 and 4-2 showing work of Bell et al (2007). As you can see the population average birth weight effect of PM2.5 is estimated to be about 80 g, and the effects associated with NO2 and CO come out at about 32-35 grams.

Figure 1: Relationships Between Reported Cigarettes Smoked per Day, Average Birth Weight, and Infant Mortality



Data Source: National Center for Health Statistics. 1996.[1] 1990 Birth Cohort Linked Birth/Infant Death Data Set, NCHS CD-ROM Series 20 No. 6, SETS Version 1.22a, issued May 1996.

Figure previously appeared in Hattis, D. "Role Of Dosimetric Scaling And Species Extrapolation In Evaluating Risks Across Life Stages. IV. Pharmacodynamic Dosimetric Considerations." Draft Report to the U.S. Environmental Protection Agency Under RFQ No. DC-03-0000, January 2004.

Table 1: Basic Birth Weight Reduction Results Based on County-Average Air Pollutant Exposures During Gestation for 358,504 Babies in Massachusetts and Connecticut, Evaluated with Single-Pollutant Models, Controlling for Confounders[2]

Air Pollutant	Grams Reduction Birth Weight per Interquartile Exposure Range	Lower 95% Confidence Limit (g)	Upper 95% Confidence Limit (g)	Mean and Std Dev Exposure	Interquartile Exposure Range	Exposure units
NO_2	8.9	7	10.8	17.4 ± 5.0	4.8	ppb
CO	16.2	12.6	19.7	656 ± 180	303	ppb
SO_2	0.9	-2.6	4.4	4.7 ± 1.2	1.6	ppb
PM_{10}	8.2	5.3	11.1	22.3 ± 5.3	7.4	µg/m3

[1] Please note: This is missing from the reference list.
[2] Can some of the highlighted information be put into a table note to shorten the table title?

$PM_{2.5}$	14.7	12.3	17.1	11.9± 1.6	2.2	µg/m3

Source: Bell et al. (2007).

Table 2: Implications for Population Aggregate Birth Weight Changes of the Bell et al. (2007) Results for Pollutant Potencies (gram Reduction in Mean Baby Weights Per Unit Exposure During Gestation) and Suggested Population Aggregate Impacts on Birth Weights[3]

Air Pollutant	Indicated Potency in g Birth Weight Reduction per ppb Gas or (for Particles) µg/m3	Lower 95% Confidence Limit on Potency	Upper 95% Confidence Limit on Potency	Suggested Population Aggregate Effect (g/baby) (Potency x Mean Exposure)
NO_2	1.85	1.46	2.25	32
CO	0.053	0.042	0.065	35
SO_2	Non-significant			
PM_{10}	1.1	0.7	1.5	25
$PM_{2.5}$	6.7	5.6	7.8	80

- Fetal growth restriction is a common toxicological finding in reproductive/developmental studies that I think has not been given the attention it deserves by existing EPA and other risk assessment practices.

- As it happens, a relatively linear dose-response for fetal growth restriction, as in this case, is not uncommon for this response in animal studies; and recent studies in the air pollution context and with cigarette smoking indicate that it is a quite sensitive parameter in humans with potentially serious implications for infant mortality and a variety of developmental endpoints. I would urge EPA to select a relatively low benchmark response level for this endpoint, perhaps 1% or less.

Kacew The use of an increase in relative liver weight > than 10% was justified as a critical endpoint as this manifestation occurred in 2 species and was dose-related. In addition, the changes in liver weight were associated with changes in serum enzymes indicative of liver function, liver constituents such as cholesterol and bile acids as well as evidence of histopathological alterations. These parameter changes strengthened the use of liver as the critical target tissue.

[3] Can this table title be shortened?

B-3. Hepatocellular vacuolization was observed at the lowest dose in the principal study (NTP, 2004). This effect was not selected as the critical effect for the determination of the POD for derivation of the subchronic and chronic RfDs. Please comment on the rationale and justification for not selecting this endpoint as the critical effect.

Allen	The reasons given for not picking vacuolization as the critical effect may benefit from some slight refinement. It is stated that vacuolization can be either a normal response or one of the four common types of chemical-induced injury (p. 79). So it seems that the crux of the matter is determining whether or not the vacuolization observed in the NTP study was the former or the latter, and the argument should be focused on factors relevant to making that distinction and, apparently, determining that in this case the observed vacuolization did not represent injury. So, I have to wonder if the comments that vacuolization was not observed consistently across species (p. 79, lines 18-19) and that the severity was not dose-dependent (p. 79, lines 22-23) support that contention. This is not my area of expertise, but if that is the basis for the argument, then a tighter connection between those observations and why they support the decision not to consider vacuolization as the critical effect in this case should be attempted. Alternatively, EPA could argue that vacuolization is such an early indicator (even if it is an indicator of injury) that the clinical relevance is not such that one would base a POD on it. The argument here would be that the "risk" (defined purely in terms of its probability of occurrence relative to unexposed animals) for this early indicator is not the risk one wants to use to derive health-protective values for humans. Rather, an indicator (such as liver weight change) that is more clearly indicative of health hazards with clinical significance should be the basis for such derivations. If one could link the degree of change in the early event (vacuolization) to the level of change in the later, clinically significant event, then one could determine the "risk" level (RV) for that earlier event that is associated with the change of interest (e.g., a 10% risk level) for the later event and use RV as the POD. But in this case, there is no need to do so, because the NTP study includes endpoints (such as relative liver weight) that can be analyzed directly.
Bruckner	The document's authors presented a logical, comprehensive, justification for not selecting hepatocellular vacuolization as the critical effect. Did NTP (2004) specify the lobular distribution of the vacuoles? Centrilobular fatty vacuolization is a common manifestation of cytotoxicity by carbon tetrachloride and other halocarbons that undergo metabolic activation, as cytochrome P450s (CYPs) such as CYP2E1 are present in largest amounts in the centrilobular area.
Dekant	The rationale developed by EPA is well justified. The effect is inconsistent and does not show a dose-dependence. In my opinion, the increased liver weights are more appropriate as PODs.
Hattis	I think EPA's reasoning here seems reasonable.
Kacew	Although hepatic vacuolization was found at a lower dose the rational for not using this manifestation as a critical effect to derive the oral subchronic and chronic RfD is justifiable. It is correct that vacuolization occurs under normal circumstances and is not necessarily an adverse effect. In fact vacuolization occurs frequently in response to various drugs including chlorphenteramine, disobutamide, chorcyclizine (compounds known to induce phospholipidosis). The vacuolization does not appear to alter any biological functions and is reversible upon drug treatment. In agreement with this report the biological relevance of hepatic vacuolization is not known and may not even be a critical response to 1,1,2,2-

tetracholroethane.

B-4. The subchronic and chronic RfDs have been derived utilizing benchmark dose (BMD) modeling to define the point of departure (POD). All available models were fit to the data in both rats and mice for increased absolute and relative liver weight, increased incidence of hepatocellular cytoplasmic vacuolization (rats only), increased levels of ALT, SDH, and bile acids, and decreased fetal body weight. Has the BMD modeling been appropriately conducted? Is the benchmark response (BMR) selected for use in deriving the POD (i.e., one standard deviation from the control mean) scientifically justified? Please identify and provide the rationale for any alternative approaches (including the selection of the BMR, model, etc.) for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

Allen

The use of the BMD approach for selection of the POD is appropriate. I have several comments about the BMD modeling as it was actually carried out.

First, I cannot understand the a priori elimination of the two highest doses from the BMD analysis for all endpoints. Typically, dropping of doses is done only when issues of model fit are encountered, and even then they should have some strong justification. The reasons given (bottom of p. 80 to top of p. 81) do not seem like sufficient justifications. The body weight decreases may or may not indicate that the MTD was exceeded, but how does that impinge on the analysis of endpoints whose changes may be what is causing the decreased body weights. Certainly, for relative liver weight, body weight changes have been accounted for. The comment about nonmonotonicity of the relative liver weight endpoint (which really only appears to be true for male rats and not for female rats or either sex of mice; see Tables 4-2b and 6-6b) is basically a non-sequitur: data sometimes do show nonmonotonicities, but that does not mean that they "do little to inform" the dose-response shape. In fact, EPA has included nonmonotonic data in the dose-response analyses for this assessment. Even if this is considered a problem (which would be revealed by modeling all the data), it is not clear that the two highest doses are the ones that one might consider "erroneous;" it is possible that the third highest dose (one that was retained in the EPA analysis) is the problematic one (again, only in male rats does this issue arise). And this can not even be determined until and unless the overall dose-response pattern is analyzed. One of the strengths of dose-response analysis is that it considers the overall pattern as opposed to the observations at single doses (an issue that is illustrated in the extreme by the late and not-lamented NOAEL approach for defining PODs).

This a priori dropping of the highest two doses before analysis leads to some ludicrous statements in this document. When discussing the SDH data in female rats, it says that the modeling was "ultimately, attempting to fit a negative dose-response curve" (p. B-36, lines 3-4). When discussing the bile acid response in female rats (p. B-44) the document states that the modeling fits a "decreasing function of dose for the dose-response curve up to 80 mg/kg-day" (line 8). But in both of these instances, these statements are only "true" because the modeling was forced by this a priori decision to ignore the doses where a positive response was observed. So rather than getting nonsensical decreasing dose-response results, the analysis of all the data would have shown an overall positive trend, but one that was essentially flat up to around 80 mg/kg-day, and for which a valid BMD and BMDL could have been obtained that would have shown the (much higher) doses at which there was a change in response of concern for these endpoints.

Other issues (of varying importance) that I noted in the sections on the BMD analyses (and elsewhere):

- The phrase "statistically significant" is used repeatedly in the document. But I did not see where that was defined, and it appears to have been used rather loosely and inconsistently in some places. For example, on p. 76 (line 22) decrease in body weight was said to be statistically significant, but the parenthetical "(<10%)" gives the

impression that that is because of the magnitude of the change in body weight, when of course the magnitude of the change is not really (or not only) what determines whether it is statistically significant. There seems to be a similar problematic concatenation of these ideas on p. 35 (lines 27-28) where is states that a NOAEL was determined "using statistical significance and a 10% change as the criterion [emphasis added – a singular noun] for an adverse change in maternal body weight. Then on p. 38 (line 19) it says "statistically significant ($p < 0.10$)…" but that does not seem to accord with other uses of the phrase "statistically significant" (see p. 54, line 14). A strict definition of what the document means by statistical significance should be given once and adhered to throughout. Or else, the p-values associated with statistical tests should just always be given and the reader can judge what s/he thinks about significance.

- p. 93, line 17. This says BMDS version 1.4.1 was used. Elsewhere in the document it was indicated that version 2 was used.

- p. 93, line 27. The statement here is that more extreme results (higher or lower) could have been obtained by picking other models for the selected endpoint. That does not appear to be the case; when the same (apparently appropriate) representation of the variance is selected, the other models only give higher (not lower) PODs.

- There are no figure numbers for all of Appendix B.

- In at least two instances (Tables B-1 and B-2), the results for the quantal linear model are reported incorrectly. In Table B-1, the results for the linear model must match those of the first-degree multistage model; they do not. In Table B-2, the fit p-value and AIC for the linear model must be worse than that for the third-degree multistage model (or else the selected multistage model would be of degree one); they are not.

- The entire discussion of model selection on p. B-2 does not make any sense. On lines 7-9 it says "these models [referring to those that actually fit the observed responses] do not inform the dose-response between the 20 and 40 mg/kg-day dose group [sic] and, combined with perfect model fit, may lead to the introduction of model uncertainty." First, it is not any models that do not inform the dose-response; it is the data that fail to provide information. What we really have here is a case where these data by themselves do not tell us anything about where the BMD is, between 20 and 40 mg/kg-day (and even that is not a certainty), where there were 0% and 100% response rates, respectively. So why would one select a model that fits the observations worse than another model? Yes, there is a greater amount of uncertainty associated with these data, but that is not "because of the uncertainty provided by the models that provided perfect model fits but were uninformative." The only reason that the selected multistage is more sensitive (has the lowest BMDL) is because that model is constrained to fit the data in a certain way, i.e., with a curve that rises above 0 response at a lower dose, at the expense of missing (mis-predicting) the response rates at the two dose that would appear to bracket the BMD (20 and 40 mg/kg-day). And that model only looks to be "informative" because of those same constraints on its shape. There is not much model uncertainty here; once the worse-fitting multistage and linear models are excluded, all the models that fit nearly perfectly are very consistent. The uncertainty here is not model uncertainty; it is uncertainty associated with a basic data gap.

- The treatment of models that have as many parameters as observations (see, for example Table B-5) can be improved. While, in general, it is frowned upon to have as many parameters in the model as there are data points, it need not be the "kiss of death" that this document seems to imply (see, for example, footnote h to Table B-7). First of all,

	when there are no degrees of freedom to assess fit, it is good practice to note whether the model actually passes through all of the data points. If the model does not (and that sometimes happens), then it is almost always the case that the model should not be used. But, if it does pass through all the data points, then it is still a good model, just maybe over-specified and certainly one from which one might want to try to reduce the number of parameters. However, and more importantly, there is no reason to exclude it from consideration for the POD derivation. Remember that the models are implying something more than just the responses at the data points; they are providing predictions of responses are all other dose levels. I would certainty prefer a model with "too many parameters" that got the shape right than one that had fewer parameters and therefore did not characterize the dose-response pattern correctly. Besides, there will be other criteria (including comparisons of AICs) that might rule out these "over-parameterized" models. This is the case with the modeling results reported in Table B-7, where the model with no degrees of freedom for the goodness-of-fit evaluation would not have been selected on the basis of a larger AIC. • There are some tables (e.g., Tables B-5 and B-6) where the AIC is not reported, so the reader cannot corroborate the model choice that EPA has made. • The polynomial model fit to serum ALT in female rats (Table B-8) is nonmonotonic. Is that really a reasonable dose-response shape to be using for determining the POD? This again might be a case where consideration of the doses that were excluded a priori would have a significant impact on model choice and POD estimation. • The analysis of the fetal weight data has several issues. First, why did EPA deviate here from its policy of picking the model with the lowest AIC? The rationale given is that they picked the model with the lowest BMDL. That is not consistent with the policy as stated in the guidelines (the difference in BMDL estimates over models is less than a factor of 1.4) or as applied to the other endpoints. Second, the headings for the columns giving the BMD and BMDL are not consistent with the footnotes f and g in Table B-13. This is because the definition of the BMR has changed here without any discussion or acknowledgement that it has done so; aside from an easily overlooked notation in Table 5-1 of the BMR, the different definition of the BMR is not presented in the document. Moreover, this definition of the BMR for the fetal weight data does not seem to be appropriate; the modeling results shown on pp. B-51 to B-53 indicate that the BMR definition actually used is 5% "absolute risk" which corresponds to a change of 0.05 units from the control mean. This is not a relative change; it is simply a 0.05 g decrease in the mean average-fetal weight. I know of no basis for selecting that value for the BMR. Since the modeling of this endpoint is just like any other continuous endpoint, I would recommend using the same BMR based on a 1-standard-deviation change in the mean.
Bruckner	The BMD modeling appears to have been conducted appropriately. Again, as described above, I do not concur with selection of increased relative liver weight as the response to model. The other modeling choices and assumptions seem reasonable.
Dekant	Apparently, the analysis was conducted along standard procedures
Hattis	(consider Allen's comments and analysis in detail) In the light of Dr. Allen's premeeting comments I would recommend that EPA at least show

	earlier results with the highest doses and show the lack of fit that led the analyst to make the dose exclusions that were made. I agree that it is probably not correct to exclude the higher doses for all endpoints in summary fashion without analyzing the specific fits for different endpoints, if that is what was done in this case.
Kacew	The BMD has been conducted appropriately. The BMR selection is scientifically sound. I am not aware of any alternative approaches.

B-5. Please comment on the selection of the uncertainty factors applied to the POD for the derivation of the RfDs. For instance, are they scientifically justified? If changes to the selected uncertainty factors are proposed, please identify and provide a rationale(s).

Please comment specifically on the following uncertainty factor:

- **A database uncertainty factor of 3 was used to account for the lack of oral reproductive and developmental toxicity data for 1,1,2,2-tetrachloroethane. Please comment on whether the application of this uncertainty factor has been scientifically justified.**

Allen

The uncertainty factors applied in this case appear to be adequate. They do not depart much from the standard factors used when no PK data are available. I personally have a hard time selecting or justifying any particular value for the data base uncertainty factor. The chosen value of 3 may be appropriate given the lack of certain types of reproductive studies. On the other hand, the results of the available developmental toxicity study do seem to indicate that those types of effects are likely not to be the drivers of risk for 1,1,2,2-tetrachlroethane.

With respect to the chronic RfD and the uncertainty factor of 3 for extrapolating subchronic observations for chronic exposure scenarios, I would have liked to see more of a comparison of the resulting RfD to the observations and (admittedly quite uncertain) predictions from the NCI (1978) study. This would have been an opportunity to use the NCI data in the limited way that they deserve and to directly address the magnitude of this specific uncertainty factor.

Though this particular question did not ask about the uncertainty write-ups in particular, I feel I need to comment on those. Section 5.3 on uncertainties appears to be merely a restatement of the features that contribute to the valuation of the standard uncertainty factors (animal-to-human, inter-individual variability, etc.). What is needed is a consideration of what additional, real uncertainties are present. If there are none (if the studies are all great, the modeling is not an issue, nor is the choice of dose metric and critical response) then say so and be happy. But if there are real concerns that might materially impact the results of the assessment (e.g., is using the most sensitive species a problem?) then those need to be listed.

Here and elsewhere I was bothered not to have seen a more comparative approach used. 1,1,2,2-tetrachloroethane has major metabolites (dichloroacetic acid, trichloroethylene, perchloroethylene) that have been subject to risk assessments of their own. How do the results of those assessments compare to those derived here for 1,1,2,2-tetrachloroethane? I realize that the exact, quantitatively characterized pathways of 1,1,2,2-tetrachloroethane metabolism may not have been developed, but there must be a sense that can be derived of consistency across all of these compounds. For example, if the risk estimates derived here for 1,1,2,2-tetrachloroethane are much less than what would have been estimated for the amount of dichloroacetic acid produced by that much 1,1,2,2-tetrachloroethane (even if that amount is only roughly characterized) then this would increase uncertainty (and maybe not only for 1,1,2,2-tetrachloroethane). Conversely, if the risk estimates for 1,1,2,2-tetrachloroethane are substantially greater than would be estimated from the analyses of dichloroacetic acid, trichloroethylene, or perchloroethylene, then some explanation would be needed for that.

The bottom line is that there appear to be several opportunities for cross-chemical comparisons that could contribute to understanding the uncertainties in the 1,1,2,2-tetrachloroethane risk estimates. I have not seen any such comparisons.

Bruckner

As noted above, I believe the point of departure should be based on the dosage (i.e., NOAEL = 80 mg/kg) required to cause elevation of serum ALT and SDH activities. In light of the observed decreases in body weight, increased relative liver weight may not be a toxicologically-

	significant effect. It is standard practice to use a default interspecies uncertainty factor (UF) of 10 when there is no information to assess toxicokinetic (TK) or toxicodynamic differences between the test animals and humans. Although this is the case for TET, there is a considerable amount of information about the TK of many closely-related halocarbons [e.g., trichloroethylene (TCE), perchloroethylene (PCE), chloroform, 1,1,1-trichlorothane] in rodents and humans. It is well established that the rank order of metabolic activation of the compounds is as follows: mice >> rats > humans. Therefore, the 3.3X TK component of the interspecies UF of 10 could be removed, resulting in a value of 3. U.S. EPA (2008) recommended use of an interspecies UF of 3 to derive a RfD for PCE, based on a neurotoxic endpoint. EPA (2009) advocated an UF of 3 extrapolating from rodent inhalation data for trichloroethylene to humans. An UF of 3 is used by EPA (2003) in calculating a chronic RfD for dichloroacetic acid. The intraspecies UF of 10 is reasonable, as is the database UF of 3. A relatively wide variety of tissues and toxicity parameters have been evaluated in orally-dosed mice and rats, though a 2-generation reproductive study is lacking. The 3-fold UF is reasonable to use to extrapolate from the subchronic study (NTP, 2004) data to chronic exposures. Only modest hepatic morphological changes were seen by the NCI (1978) in rats in its chronic bioassay. The lack of progression of severity of hepatotoxicity with repetitive dosing may be attributable to TET's ability to inhibit its own metabolism.
Dekant	The selected uncertainty factor and its justification are acceptable. As BMD-modeling was used, no correction factor for extrapolation from a LOAEL to NOAEL is required. The additional factor of 3 to account for extrapolation from subchronic to chronic exposure is widely accepted in regulatory toxicology and justified.
Hattis	I think EPA's reasoning here seems reasonable and the analysis reasonably standard.
Kacew	The use of uncertainties was appropriate. The use of uncertainty factor of 3 for lack of oral reproductive and developmental toxicity data for 1,1,2,2-tetrachloroethane is appropriate.

(C) Inhalation reference concentration (RfC) for 1,1,2,2-tetrachloroethane

C-1. An RfC for 1,1,2,2-tetrachloroethane has not been derived. Has the scientific justification for not deriving an RfC been described in the document? Please identify and provide the rationale for any studies that should be selected as the principal study. Please identify and provide the rationale for any endpoints that should be considered in the selection of the critical effect.

Allen	In general, I understand and agree with the decision not to derive an RfC. Here, as indicated in the response to the last question, comparison to metabolically related compounds (dichloroacetic acid, trichloroethylene, or perchloroethylene) and the inhalation risk estimates derived for those compounds might have been useful. Such information could certainly have been included in the discussion of the uncertainties associated with not deriving an RfC.
Bruckner	There is not a suitable inhalation study to provide data from which a RfC can be derived. The document's authors have done a good job presenting an overview of the design, findings and problems of the inhalation studies that have been reported. I agree with the document's authors that a PBPK model could not be used, were one available, for route-to-route extrapolation. There are no inhalation TK data for TET to use in calibrating or validating a PBPK model for the inhaled chemical.
Dekant	No study performed according to toxicity testing guidelines and reporting sufficient details is available. Therefore, there is no useful basis to derive an inhalation RfC. Due to absence of data and PBPK-models,, an extrapolation from the oral toxicity data to inhalation exposure is not possible.
Hattis	I think EPA's reasoning here seems reasonable.
Kacew	The inability to derive a RfC based upon the data available is appropriate. In the studies reported the limitations were clearly presented and justified such that an RfC could not be derived.

(D) Carcinogenicity of 1,1,2,2-tetrachloroethane

D-1. Under EPA's 2005 *Guidelines for carcinogen risk assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that 1,1,2,2-tetrachloroethane is *likely to be carcinogenic to humans* by all routes of exposure. Please comment on the cancer weight of the evidence characterization. Is the cancer weight of evidence characterization scientifically justified?

Allen	This is probably one of the weakest instances of a conclusion that a compound is likely to be carcinogenic to humans, when the cancer data for 1,1,2,2-tetrachloroethane are considered by themselves. This may be even more the case since the only cancer with any significant dose-response is the liver tumor response in B6C3F1 mice, a fact that may be problematic but which is only mentioned very briefly in this document (p. 100, lines 32-35). As in responses to previous questions, I would advocate looking at the determinations for related compounds (dichloroacetic acid, trichloroethylene, or perchloroethylene) to help make a stronger case for this determination.
Bruckner	I do not concur with the Agency's conclusion that TET is likely to be carcinogenic in humans by all routes of exposure. I think it would be more accurate to characterize TET as a possible human carcinogen. Animals and humans will receive a substantially lower hepatic dose by inhalation than by ingestion, as only 20 – 25% of the cardiac output enters the liver. All of an oral dose absorbed from the GI tract into the portal circulation passes into the liver. Dermal exposure will make a modest contribution to one's total systemic dose, relative to ingestion and inhalation. See below for other reasons for downgrading TET from a likely to a possible human carcinogen.
Dekant	[no response provided]
Hattis	Yes
Kacew	With respect to the effects in the B6C3F1 mouse the cancer weight of evidence is scientifically justifiable that 1,1,2,2-tetracholoroethane is a hepatic carcinogen based upon the response in both genders and in a dose-related manner. In Osborne Mendel rats evidence of carcinogenicity was not conclusive.

D-2. A two-year oral gavage cancer bioassay (NCI, 1978) was selected as the principal study for the derivation of an oral slope factor. Please comment on the appropriateness of the selection of the principal study.

Allen	This study is the only option for deriving an oral slope factor. However, that does not mean it is a good option. This study suffers from a poor selection of dose levels (too few and too high) that apparently had to be adjusted several times during the course of the study. Exposure lasted only 78 weeks as opposed to the more standard 104 weeks. Apparently, there were also difficulties with respect to concurrent diseases (pneumonia). So, while this study may be the principal study just because it is the only option available, much more needs to be stated about its deficiencies and the resulting uncertainty. Here again, a quantitative or semi-quantitative comparison to the assessments for other related compounds (dichloroacetic acid, trichloroethylene, and perchloroethylene) can be used to highlight and/or address some of those concerns. In fact, given the issue that is just briefly mentioned in the document (p. 100, lines 32-35) related to the liver tumor response in the B6C3F1 mouse, I am not at all sure that any slope factor should have been derived from this study. I would have been satisfied with a decision not to derive an oral cancer slope factor for 1,1,2,2-tetrachloroethane.
Bruckner	The NCI (1978) bioassay must be used as the principal study, as it is the only complete bioassay of TET.
Dekant	The study used is the only one available. Since there is no mechanistic information on mode-of-action of 1,1,2,2-tetrachloroethane induced liver tumors, a linear extrapolation is mandated based on US EPA guidelines. The uncertainties in the assessment are well characterized, but the section could be expanded. A lot of information on effects of the major metabolites of 1,1,2,2-tetrachloroethane trichlorethene, trichloroacetic acid, trichloroethanol and dichloroacetic acid is available. This information should be briefly described and integrated in the assessment
Hattis	This seems to be the only relevant study available. It is approprtiate, although there are concerns that gavage dosing delivers chemical in a short term bolus; and this might not give the same results as a dietary or other oral dosing method that delivered the test chemical more gradually over time.
Kacew	The use of the 2-year NCI (1978) study was well-designed and appropriate to derive the oral slope factor.

D-3. An increased incidence of hepatocellular carcinomas in B6C3F1 mice was used to estimate the oral cancer slope factor. Please comment on the scientific justification of this analysis. Has the BMD modeling been appropriately conducted?

Allen

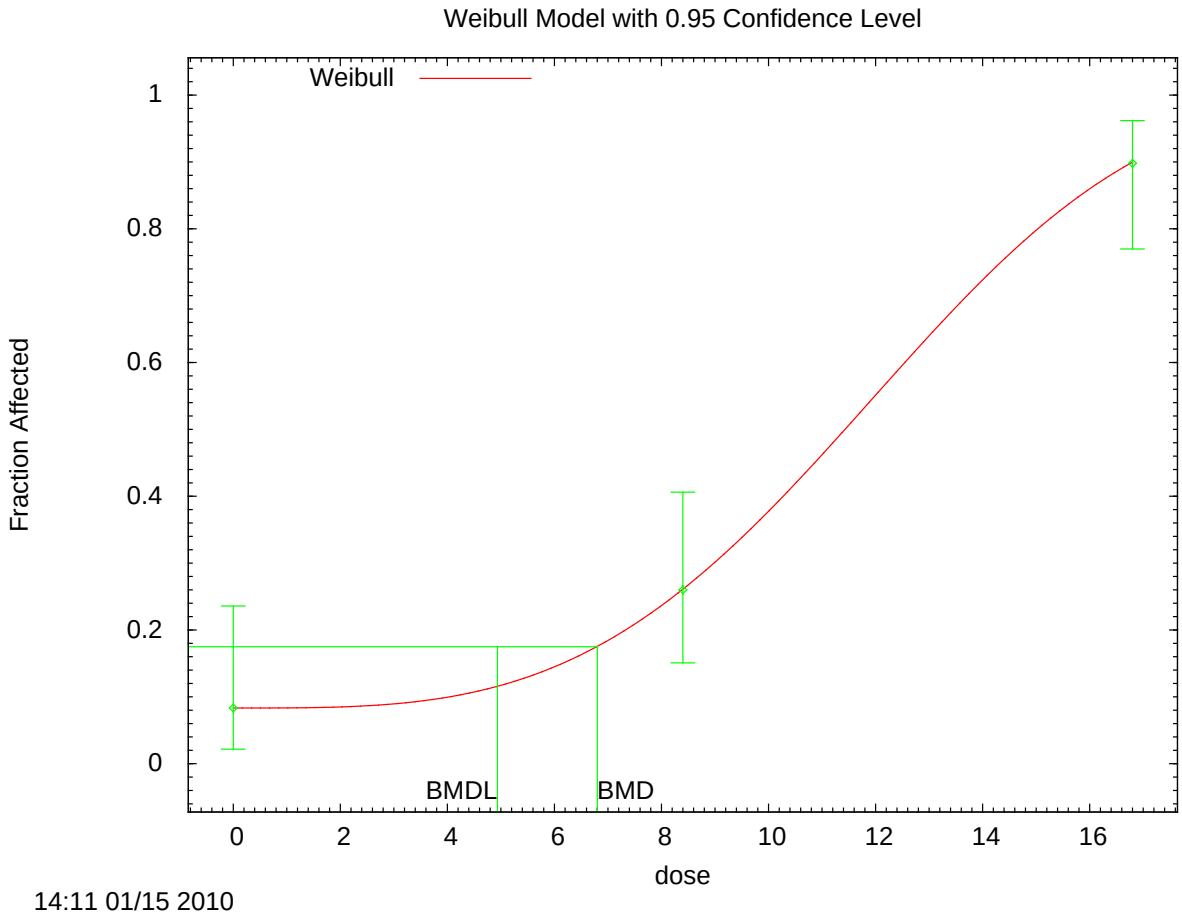
Comments about the concern over the relevance of this specific tumor have been expressed above.

The BMD modeling is, in general, adequate.

Clearly, there is a typo in Table C-2, because the reported BMDU is less than the reported BMDL.

There should be more information presented about the modeling of the male mouse response, including a graph of the fit of some of the models. Even though poor fits are reported, that should not, in my opinion, mean that they automatically get excluded from consideration.

In particular, the models for which "NA" is reported for the goodness-of-fit p-value need to be described further: did they actually fit all of the data points, even if they used "too many" parameters? If so, they certainly would be candidates for deriving a POD, much preferred over the models that did not fit well (even if they had degrees of freedom for evaluating fit). The fit of the Weibull model is shown here:



This model (among others) fits the data perfectly well and gives valid BMD and BMDL estimates that

	can (and should) be used as candidate PODs. In this instance, the female POD-candidate is lower and would still be selected as the POD, but the point is that these results should not be characterized by saying "the BMD modeling of the male did not achieve adequate fit for any of the dichotomous models" (p. C-1, lines 17-18). In the statement of the uncertainties related to the cancer assessment, too little is said about the issues of mode of action, at least as it is delineated in this document. I have yet to see an IRIS assessment that failed to say that there was inadequate information to rule out genotoxicity, or in fact to draw any conclusion regarding mode of action. Given the preponderance of genotoxicity tests that suggest that 1,1,2,2-tetrachloroethane is not genotoxic, and the statements in the document that appear to conclude that 1,1,2,2-tetrachloroethane is a promoter and not an initiator, the question must be asked, how much information would be enough information to make a determination one way or the other? As it stands, I would prefer a UF approach for the 1,1,2,2-tetrachloroethane cancer assessment. But again, I think that information obtained from relevant, metabolically related compounds (dichloroacetic acid, trichloroethylene, and perchloroethylene) should have been included in this assessment.
Bruckner	There are substantial uncertainties about the human relevance of the NTP (1978) findings. As pointed out elsewhere, mice and other rodents metabolically activate a considerably larger proportion of high doses of halocarbons to reactive metabolites than do humans. Therefore, rodents experience more severe hepatocellular injury, greater formation of covalent adducts, and very likely a higher cancer incidence. Pahler et al. (1999) and Volkel et al. (1998), for example, subjected rats and humans to equivalent PCE inhalation exposures. The rats absorbed 7 times more PCE, excreted significantly larger quantities of urinary metabolites, and exhibited substantially higher levels of covalent protein adducts in their blood. As I have pointed out elsewhere in my comments, both sexes of the B6C3F1 strain of mice have a very high spontaneous liver cancer incidence. Haseman et al. (1998) reported that male B6C3F1 control mice have a 42% liver cancer incidence. This incidence is increasing over the years, and may not have been so high when the NIH bioassay of TET was conducted. NTP has held a series of workshops to explore replacing both the B6C3F1 mouse and the F-344 rat in future bioassays (King-Herbert and Thayer, 2006). It is noted in the Toxicological Review for TET that dichloroacetic acid (DCA) appears to be a major metabolite, that TCE and PCE are also metabolites, and that all are liver carcinogens in mice and/or rats. The authors should point out that DCA and trichloroacetic acid (TCA) are metabolites of both TCE and PCE, so the hepatocarcinogenic effects of these metabolites should be additive. Nevertheless, it is important to point out there is no quantitative data on the quantities of these metabolites formed by rodents or humans. TET may also be metabolically activated by a glutathione conjugation pathway. This seems unlikely judging from TET's structure, but no one has apparently studied this. Mice produce substantially larger quantities of DCA than rats (or humans). The authors should also point out that DCA and TCA are not genotoxic. These metabolites alter gene expression in hepatocytes, but only as long as they are present in sufficient amounts in the cells (Bull, 2000). DCA is rapidly metabolized, and TCA is eliminated within a day or so. As detailed in the Toxicological Profile summary, genotoxicity studies provide only limited evidence of a genotoxic mode of action. The majority of the considerable number of in vivo and in vitro experiments yielded negative results. In light of the foregoing, a weight-of-evidence assessment does not lead to the conclusion that TET is likely to be genotoxic and that a linear cancer risk assessment model should be employed. It seems more likely that TET may act as a tumor promoter (Story et al., 1986). This would explain the high incidence of liver cancer in B6C3F1 mice, a strain which appears to have clones of initiated or precancerous hepatocytes. Regenerative hyperplasia is a more likely mode of action than genotoxicity. The former would require chronic exposure to TET doses high enough to cause ongoing hepatocellular death and proliferation. NCI (1978) saw evidence of liver cytotoxicity and necrosis in its chronic investigation. The dosage regimen utilized by NCI (1978) was of limited relevance to real-life oral human exposures to TET. Oral bolus administration of TET and other halocarbons will produce more pronounced

	hepatotoxicity than when the chemicals are ingested in divided doses over the course of the day. Sanzgiri et al. (1995), for example, gave the same doses of carbon tetrachloride (CC14) to rats by corn oil gavage and over 2 hours by gastric infusion. Blood CC14 levels and hepatic damage were significantly higher in the gavage group. La et al. (1996) saw marked necrosis and ensuing proliferation of hepatocytes of mice given 1,2,3-trichloropropane in corn oil by gavage, but no such effects in mice which consumed the same daily doses in their water. In such instances, halocarbons are rapidly/extensively absorbed from the GI tract and delivered to the liver via the portal venous blood in amounts high enough to exceed the capacity of hepatocellular protection and repair processes. Chloroform, 1,1- and 1,2-dichloroethane have produced high incidences of hepatocellular carcinoma when administered to B6C3F1 mice by corn oil gavage. Jorgenson et al. (1985) and Klaunig et al. (1986) found no evidence of such tumors when comparable doses were supplied in the animals' drinking water. It should also be recognized that administration of large quantities of corn oil promotes lipid accumulation and lipoperoxidative damage of hepatocytes. Corn oil itself is believed to be tumorigenic in rats and humans, through a number of mechanisms including increased expression of protooncogenes, decreased apoptosis, mitogenesis, etc. (e.g., Rusyn et al., 1999; Wu et al., 2004; Solanas et al., 2009). The factors in the four preceeding paragraphs should be discussed in a substantially expanded Uncertainties section.
Dekant	Apparently, the modeling was performed according to a standard procedure. Uncertainty likely is high due to the use of an old study in a mouse strain with high background. As indicated above, inclusion of more information on the metabolites may further support the assessment.
Hattis	I replicated the finding that a simple 1 stage model will not fit the male data. Increasing to two stages would exhaust the degrees of freedom available and therefore would not allow any meaningful testing of fit. I also was able to fit the female data very adequately (P = 0.38) using my own software and derived a similar MLE slope (0.128 per mg/kg-d). Therefore it seems to me that the modeling is appropriate.
Kacew	The use of the B6C3F1 to estimate the oral cancer slope factor based upon the increased incidence of hepatocellular tumors was justified and appropriate. The BMD modeling was conducted appropriately.

Additional Reviewer Comments

Additional Comments by Wolfgang Dekant

FURTHER COMMENTS

Page 7. Metabolic scheme. How well supported is the observation that tetrachloroethene is a metabolite of 1,1,2,2-tetrachloroethane? Formation of tetrachloroethene would involve an abstraction of two hydrogen atoms, which is highly unlikely from the viewpoint of biotransformation reactions. Both enzymatic (by a P450-dependent mechanism) and non-enzymatic formation of trichloroethene are considered much more likely to account for the formation of trichloroacetic acid and trichloroethanol.

Additional Comments by James Bruckner

Specific Comments

p. 5, pgr. 2: It should also be pointed out that the rapid, extensive oral absorption of 1,1,2,2-tetrachloroethane (TET) in mice and rats would also be expected to occur in humans.

p. 5, line 28: The dosage vehicle should be included. See addition to text.

p. 6, pgr. 1: The findings of Morgan et al. (1970) do not conflict with those of Lehmann et al. (1936). Systemic absorption of volatile organic chemicals (VOCs) is initially very high, but diminishes over time of exposure as the chemical accumulates in the body and blood returning to the pulmonary circulation contains higher and higher levels. The findings of 40 – 60% systemic retention are quite typical of this class of compounds.

p. 6, lines 11 – 17: The greater systemically absorbed dose in mice (than rats) results primarily from their larger cardiac output, higher respiratory rate, and greater rate of TET metabolism.

p. 6, lines 29 – 34: Tissue:air partition coefficients (PCs) alone do not directly inform us about TET's propensity to partition into tissues. Gargas et al. (1989) published both blood:air and tissue:air PCs. These can be easily be used to derive tissue:blood PCs. These values and rate of blood flow dictate TET uptake by different tissues.

p. 6, pgr. 4: It should be recognized in this instance that nonvolatile radioactivity likely represents TET metabolites, including metabolites that have been incorporated into endogenous cellular components.

p. 8, lines 14 – 18: Based on the findings of Yllner et al. (1971), the range of values in line 14 should be changed from ≥ 68% to 68 – 95 %. The % metabolized will depend, of course, upon the administered dose, species and gender.

p. 9, line 34: See recommended addition to the sentence.

p. 10, lines 15 & 16: It would be informative to compare TET's estimated V_{max} of 12 mg/hour with *in* vitro V_{max} values of some other common halogenated short-chain aliphatic hydrocarbons (halocarbons), in order to gain some perspective on the TET's relative metabolic rate.

p. 11, lines 21 – 25: Specify the doses of TET given orally by Milman et al. (1984) and by Mitoma et al. (1985). Administration of high doses would be expected to result in high carcass retention due to metabolic saturation.

p. 12, line 16: What is meant by the term "system state"?

p. 41, lines 34 – 38: Did Horiuchi et al. (1962) report their histological findings?

p. 69, line 9: See my previous comments about systemic absorption of 40 – 60% of inhaled VOCs by rodents, once near steady-state is reached.

p. 69, line 31: All halocarbons require metabolic activation (via CYP450-mediated oxidation and/or glutathione conjugation and mercapturic acid formation) in order to exert cytotoxicity/mutagenicity. The evidence summarized here indicates that TET is no different.

p. 70, lines 25 – 38: It is important to recognize that very high oral doses (≥ 1 g/L water) of dichloroacetic acid (DCA) are required to produce liver tumors in mice. There are apparently few quantitative data from which to determine how much DCA is formed from different doses of TET. It is well established that mice produce modest amounts of DCA from trichloroethylene (TCE) and perchloroethylene (PCE). Barton et al. (1999) concluded from predictions of a PBPK model that DCA levels formed in TCE-exposed mice were insufficient to cause liver tumors. Rats produce very little DCA from these VOCs. It is not clear whether humans produce any DCA, as DCA itself is very rapidly metabolized (NRC, 2009). In light of the foregoing, this paragraph should be revised to reflect this information and to stress that DCA may contribute to TET-induced liver tumors in B6C3F1 mice. TCE and PCE are also liver carcinogens in this strain of mouse, though the amounts formed from TET relative to DCA have apparently not been established. Both TCE and PCE are believed to exert their liver carcinogenicity in B6C3F1 mice via TCA and DCA.

It is implied in lines 31 and 34 that TCE and PCE were not found to produce statistically significant increases in liver tumors in rats, because of early mortality/inadequate study designs. This is not the case. TCE and PCE were not liver carcinogens in any strain of rat in any cancer bioassay, including several that are not cited here. This is attributed to the lower metabolic activation capacity of rats, and to the apparent absence of clones of precancerous hepatic cells that may be responsible for the high incidence of hepatocellular carcinoma in B6C3F1 mice (Haseman et al., 1998; King-Herbert and Thayer, 2006).

p. 71, lines 1 & 2: The preponderance of evidence from *in vivo* and *in vitro* genotoxicity experiments, as described in subsection 4.5.1, is negative. The summary, in line 26 of page 53, states "genotoxicity studies provide limited evidence of a mutagenic mode of action". These conclusions should be presented here at the top of page 71.

p. 71, lines 3 – 9: It should be noted here that doses of TET and other VOCs absorbed from the GI tract directly enter the liver via the portal circulation. Inhalation of the same dose results in a substantially smaller amount of VOC reaching and producing adverse effects in the liver. Inhaled carbon tetrachloride ($CC1_4$) and 1,1-dichloroethylene have been shown to be much less acutely hepatotoxic to rats than equivalent oral doses (Sanzgiri et al., 1995; Bruckner et al., 2010). Thus, adverse effects of inhaled and ingested TET may be the same qualitatively, but not quantitatively.

p.74, lines 6 – 8: It is correctly stated that individuals with elevated CYP450 levels may be more susceptible to TET cytotoxicity. As explain previously, this will be true for relatively high-level (e.g., in some occupational settings) exposures, but not for low, environmental exposures.

p. 74, lines 12 – 15: It should also be stated here that TET, in sufficient doses, would protect against VOCs and other chemicals that undergo CYP450-catalyzed metabolic activation to cytotoxic and/or mutagenic metabolites.

p. 74, line 16: It should be stated here that no human or animal data are available with which to assess the susceptibility of infants or children to injury by TET when exposure occurs postnatally.

p. 74, lines 27 & 28: This introductory sentence should be rewritten. It should state that no studies have been conducted to assess the basis of differences observed in the potency of TET in male and female rodents.

p. 74, lines 30 – 32: The authors should note here that the higher body fat content of females results in higher body burdens and longer residence times (t½) for TET.

ADDITIONAL REFERENCES

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Appendix A

List of Reviewers

Peer Review Workshop of EPA's Draft Toxicological Review of 1,1,2,2-Tetrachloroethane Human Health Assessment

Holiday Inn Capitol
Washington, DC
January 27, 2010

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Appendix B

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Peer Review Workshop of EPA's Draft Toxicological Review of 1,1,2,2-Tetrachloroethane Human Health Assessment

Holiday Inn Capitol
Washington, DC
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Appendix C

Agenda

United States
Environmental Protection Agency
National Center for Environmental Assessment

Peer Review Workshop of EPA's Draft Toxicological Review of 1,1,2,2-Tetrachloroethane Human Health Assessment

Holiday Inn Capitol
Washington, DC
January 27, 2010

Agenda

8:00 a.m. **Registration/check in**

8:30 a.m. **Welcome, Introductions, Meeting Purpose & Agenda**.....*Jan Connery, ERG (contractor)*

8:40 a.m. **EPA Welcome Remarks**.....*Abdel Kadry, IRIS Program Director, EPA NCEA*

8:50 a.m. **Public Comment**.....*Jan Connery*

9:00 a.m. **General Questions**..... *James Bruckner (Chair) & Panel*

A-1. Is the Toxicological Review logical, clear and concise? Has EPA clearly synthesized the scientific evidence for noncancer and cancer hazard?

A-2. Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of 1,1,2,2-tetrachloroethane

9:30 a.m. **Oral Reference Dose (RfD) for 1,1,2,2-Tetrachloroethane**... *James Bruckner & Panel*

B-1. Principal Study: Subchronic and chronic RfDs for 1,1,2,2-tetrachloroethane have been derived from a 13-week oral gavage study (NTP, 2004) in rats and mice. Please comment on whether the selection of this study as the principal study has been scientifically justified. Please identify and provide the rationale for any other studies that should be selected as the principal study.

B-2. Critical Effect: Increased relative liver weight was selected as the critical effect for the derivation of the subchronic and chronic RfDs. Please comment on whether the rationale for the selection of this critical effect has been scientifically justified. Please provide a detailed explanation. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

B-3. Critical Effect: Hepatocellular vacuolization was observed at the lowest dose in the principal study (NTP, 2004). This effect was not selected as the critical effect for the determination of the POD for derivation of the subchronic and chronic RfDs. Please comment on the rationale and justification for not selecting this endpoint as the critical effect.

10:30 a.m. BREAK

10:45 a.m. **Oral Reference Dose (RfD) for 1,1,2,2-Tetrachloroethane** *(cont.)*..... *James Bruckner & Panel*

B-4. **Point of Departure:** The subchronic and chronic RfDs have been derived utilizing benchmark dose (BMD) modeling to define the point of departure (POD). All available models were fit to the data in both rats and mice for increased absolute and relative liver weight, increased incidence of hepatocellular cytoplasmic vacuolization (rats only), increased levels of ALT, SDH, and bile acids, and decreased fetal body weight. Has the BMD modeling been appropriately conducted? Is the benchmark response (BMR) selected for use in deriving the POD (i.e., one standard deviation from the control mean) scientifically justified? Please identify and provide the rationale for any alternative approaches (including the selection of the BMR, model, etc.) for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

B-5. Uncertainty Factors: Please comment on the selection of the uncertainty factors applied to the POD for the derivation of the RfDs. For instance, are they scientifically justified? If changes to the selected uncertainty factors are proposed, please identify and provide a rationale(s). Please comment specifically on the following uncertainty factor:

- A database uncertainty factor of 3 was used to account for the lack of oral reproductive and developmental toxicity data for 1,1,2,2-tetrachloroethane. Please comment on whether the application of this uncertainty factor has been scientifically justified.

11:30 a.m. **Inhalation Reference Concentration (RfC) for 1,1,2,2-Tetrachloroethane**..... *James Bruckner & Panel*

C-1. An RfC for 1,1,2,2-tetrachloroethane has not been derived. Has the scientific justification for not deriving an RfC been described in the document? Please identify and provide the rationale for any studies that should be selected as the principal study. Please identify and provide the rationale for any endpoints that should be considered in the selection of the critical effect.

Noon LUNCH

1:15 p.m. **Carcinogenicity of 1,1,2,2-Tetrachloroethane**..... *James Bruckner & Panel*

D-1. Weight of Evidence Determination: Under EPA's 2005 *Guidelines for carcinogen risk assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that 1,1,2,2-tetrachloroethane is *likely to be carcinogenic to humans* by all routes of exposure. Please comment on the cancer weight of the evidence characterization. Is the cancer weight of evidence characterization scientifically justified?

D-2. Principal Study: A two-year oral gavage cancer bioassay (NCI, 1978) was selected as the principal study for the derivation of an oral slope factor. Please comment on the appropriateness of the selection of the principal study.

D-3. Oral Cancer Slope Factor: An increased incidence of hepatocellular carcinomas in B6C3F1 mice was used to estimate the oral cancer slope factor. Please comment on the scientific justification of this analysis. Has the BMD modeling been appropriately conducted?

2:00 p.m. **Additional Discussion Issues** ..... *James Bruckner & Panel*

2:30 p.m. **Reviewer Final Comments** ..... *James Bruckner & Panel*

2:50 p.m. **Closing Remarks** ..... *Jan Connery & EPA/NCEA*

3:00 p.m. **ADJOURN**