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November 1, 2005

Nancy K. Kim, Ph.D.
Director, Division of Environmental Health Assessment
Center for Environmental Health
New York State Department of Health
Flanigan Square, 547 River Street
Troy, NY 12180

Dear Dr. Kim:

The Trichloroethene Panel met on Monday, August 29th and Tuesday, August 30th, 2005 at the Desmond Hotel & Conference Center, 660 Albany-Shaker Road, Albany, New York to review and comment on the New York State Health Department's draft Trichloroethene (TCE) Air Criteria Document. The panel membership (including a brief biography of each member), the charge to the panel and the agenda are attached (Attachments A, B and C respectively).

In its charge, the panel was asked to provide written responses to six questions on the TCE document and one panel member coordinated the response for each question. In addition, the panel also provided verbal comments on two questions asked about the August 23, 2005 New York State Health Department's Cancer and Birth Outcome Analysis, Endicott Area, Town of Union, Broome County, New York; those questions are also listed on the charge.

The panel's written responses to the six questions in the charge are provided in this letter. The panel developed these comments at the meeting. Although Dr. Daston was unable to attend the meeting, he provided written comments on two questions and they were available at the meeting. (Dr. Fisher left Tuesday's meeting about 4 hours before it ended and I left about 1 hour before it ended.) After the meeting the panel was given copies of the written comments developed during the meeting and their initial draft responses. They were given the opportunity to revise their initial comments, given the discussion at the meeting. The final individual responses are in Attachment D.

Although the panel did not develop written responses to the questions on the health statistics review, staff from the New York State Department of Health summarized the major points of the discussion and the panel was given the opportunity to review and comment on the summary. The written summary is in Attachment E.

The panel responses to the six charge questions are as follows:

1. **Does the discussion on animal and human central nervous system effects adequately justify development of the recommended criterion based on those effects?**

- The choice of critical studies is appropriate.

Rasmussen et al. (1993) is the appropriate critical human study, and Arito et al. (1994) is the appropriate animal study to gauge the effects of TCE on the CNS. Rasmussen et al. is a good epidemiological study. Trichloroethanol and trichloroacetic acid (TCA) in blood and urine were used as biomarkers of TCE exposure, and neurological tests used as the response. The data show a clear dose-response effect. An LOEL of 50 mg/L (TCA in urine) was observed. Arito et al. used brain electrical measurements to measure wakefulness. The data clearly show a LOEL of 50 ppmv (TCE in air). Conversion of units by the DOH in the two studies into potential air criteria gives 40 (Rasmussen et al.) and 64 $\mu g/m^3$ (Arito et al.). The close agreement between the human and animal studies increases confidence in the potential air criteria.

- The uncertainty factor of 3 for extrapolation of LOEL to NOEL may be too low.

The Arito et al. study gives an LOEL. In the draft study, the LOEL is divided by a factor of 3 to account for the fact that a NOEL was not found in this study. Some panel members thought a factor of 10 should have been used instead. The slope of the dose-response curve in Fig. 1 of Arito et al. is not steep, and extrapolation to an NOEL warrants the larger factor. Also, the factor of 3 is an estimate whose uncertainty might well encompass the more conservative factor of 10. In the justification for the factor of 3, three studies and a review are cited to give a range of factors of 1.5 to 5. However, the ratios depend on the selection of an endpoint. The endpoint of the critical Arito et al. study (wakefulness) is not included in the cited work. One panel member thought that the use of a factor of 3 instead of 10 was justified, based on professional judgment in addressing CNS toxicity of some other chemicals.

- The potential air criterion for children should consider children ages 0-2 years

The panel commends DOH for considering separately a potential air criterion for children. In light of possible effects of TCE on development, the panel recommends that DOH consider children from the ages 0-2 years, a time during which most CNS development in children occurs. Some additional factors to be considered are mass factors 3.5 kg /70 kg (newborn/adult), 12.4 kg/70 kg (2 yr old/adult), and ventilation factors (0.4 L min (0.15 L/min) (newborn/adult). One way to express this is ventilation/mass.

- The potential air criterion for children should be discussed separately from that of adults and include neuro-developmental effects.

The draft document, in the section on CNS effects, calculates an equivalent child exposure value by multiplying by the appropriate mass and ventilation factors, resulting in 2.5-fold lower potential air criterion for children. This value is then treated just as another data point in the range of values presented in table 3.2 and not considered further in the draft study. Children are a susceptible population. Child-based PBPK models for other halogenated

hydrocarbons indicate that neonates are 3 to 10-fold more susceptible to chemical toxicity via inhalation and oral routes than adults. The developing brain is more susceptible to toxins that adults. In considering childhood sensitivity, the addition of a factor to address lack of adequate data on the neurodevelopmental endpoints should be considered. There is EPA guidance on this issue.

- The draft study should address the difference between its calculation of the human equivalent LOEL from the Arito et al. study and ATSDR calculation from the same study.

The time-weighted LOEL from the Arito et al. study is 64 mg TCE/m^3. Uncertainty factors are then applied to this value to arrive at a potential air criterion of 64 $\mu g/m^3$. ATSDR (1997, Appendix A), in performing the same calculation, multiply the LOEL by a mass factor (70 kg)/(0.213 kg) (human/rat) and a ventilation factor (0.23 m^3/day)/(20 m^3/day) (rat/human) to convert LOEL from rats to human. These factors were not included in the DOH calculation. The difference between DOH and ASTDR calculations should be addressed.

2. **The data from Land et al. (1981) and DuTeaux et al. (2004) (inhalation and drinking water studies, respectively) are used to develop potential criteria for reproductive effects. Does the discussion adequately justify recommended criterion based on reproductive effects?**

- The Panel agrees that potential air criteria should be derived for the male reproductive endpoint.

The DOH document provides a good, balanced discussion of the findings and limitations of human and animal TCE studies addressing reproductive endpoints. The Panel agrees with the statement that "There is some suggestive evidence from human studies that TCE inhalation exposure may be linked to reproductive effects in both women and men." With regard to the experimental evidence in animal studies, there is sufficient evidence that trichloroethylene causes reproductive toxicity, with the evidence being the strongest for male mediated effects. The Panel therefore agrees with the decision by DOH to derive potential air criteria for the male reproductive endpoint.

- The National Toxicology Program (NTP) continuous breeding study should be considered as a basis for deriving a potential air criterion for the male reproductive toxicity endpoint.

The decision by DOH to derive potential air criteria for the male reproductive endpoint should not preclude the use for this purpose of the dose response data from the National Toxicology Program's continuous breeding study in rats for endpoints where male and female mediated effects can not be distinguished. The Panel recommends that DOH consider deriving a potential criterion from this study. The Panel does note the study will have to be carefully evaluated because, although 75 mg/kg-d was discussed as a no observed effect level, upon closer

examination this dose might be more appropriately characterized as an effect level. This issue loses importance if a benchmark dose approach is used in the derivation.

- The Panel recommends comparing oral and inhalation studies on a mg/kg-bw basis.

The dose response data for male reproductive toxicity from the various oral and inhalation animal studies are fairly consistent. Studies with fairly crude evaluation of endpoint (e.g., Land et al., 1981) or shorter duration show effects at relatively high dose levels. More sensitive studies generally show effects at lower levels. To aid in the comparison of effect levels across studies the Panel recommends the creation of a table providing observed effect and no effect doses in mg/kg-bw applied, with the length of exposure and effect seen noted.

- Studies with sensitive measures of reproductive toxicity should receive more weight than the Land et al. study in deriving potential air criteria.

The data as whole on reproductive toxicity are consistent across studies and coherent with respect to different study types, and DOH should emphasize this in the discussion. This supports the consideration for potential air criteria derivation of studies with sensitive evaluation of endpoints that may have other limitations. For example, the relatively recent inhalation study by Kumar et al. (2000, 2001a) which entailed exposure for longer periods than most other studies (12 or 24 weeks), and with more intensive evaluation of endpoint, was excluded by DOH from the consideration because the study was conducted at one dose level. This also supports the use of the DuTeaux et al. (2004) study by DOH in derivation of a potential air criterion. It also would support giving the older, less sensitive, and less reliable Land et al. study less weight in the evaluation, and the Panel recommends this be done.

- The use of TCA produced by existing PBPK models as a dose surrogate in the derivation of potential air criteria for male reproductive toxicity is a reasonable practical choice.

A series of potential air criterion was calculated using PBPK dose metrics from a model that did not specifically include the testis as a compartment. In the model, oxidative metabolism of TCE to TCA, DCA and TCOH occurs in the liver. There is a growing body of evidence that supports the notion that localized oxidative metabolism of TCE occurs in the testis, and that this gives rise to the male reproductive toxicity observed. (Metabolism of TCE in the testis may also occur for the glutathione pathway but this has not been studied.) Thus the use of dose metrics from a model that does not include testicular metabolism introduces error into the analysis. The magnitude and direction of the error is not known, although the Panel felt that the use of TCA as the dose surrogate may be biased toward overestimating dose because it has a relatively long half-life in humans compared to the rodent. The Panel therefore thought this to be a reasonable practical choice. Development of a PBPK model that would include a testicular compartment would be an experimental and computational research project, and beyond the scope of the DOH effort.

- The document should include a discussion of human interindividual variation, particular due to TCE metabolism, to explain the use of the adjustment (uncertainty) factor for that purpose in deriving potential air criteria.

An uncertainty factor of 10 is used to account for interindividual variability within humans. There is likely to be considerable variability in human response, due to TCE metabolism alone, for both formation of active metabolites and their detoxification. The Panel recommends a brief discussion of the degree of potential variability due to metabolic factors be included in the DOH document to support the use of the factor of 10. A further consideration is that the mechanism by which TCE causes testicular toxicity may be ongoing in causing effects in the general population, and other xenobiotic and endogenous exposures may be involved, thus raising the possibility of dose additivity and variable sensitivity. It would be reasonable for DOH to also discuss this issue in conveying the extent of potential variability in response as well as the extent to which the results may be conservative.

3. **The Dawson et al. (1993) data are used together with other information provided by the study authors to develop potential criteria based on developmental effects. Does the discussion adequately justify the recommended criterion based on developmental effects?**

- Major points

The major issues discussed by the panel in the area of developmental toxicity were the choice of critical study and the vulnerability during early development.

Questions addressed by the panel were:

1. Is there too much emphasis on congenital heart defects (CHD) studies and insufficient emphasis on other endpoints?
2. Is developmental neurotoxicity evaluated in sufficient detail?
3. Are fetus, infants, and children as a vulnerable life stages evaluated adequately and considered in uncertainty factors?

- Comments on Animal Studies

1. The Dawson et al drinking water studies indicated the presence of CHDs. There is considerable uncertainty in dose-response because there are three orders of magnitude between in the NOEL and LOEL dose levels. A second study (Fisher et al.) where TCE was administered by gavage, done in collaboration with the Dawson group found no evidence for CHD. A high level of CHD in control animals was found in this study suggesting a high tendency for false positives with the methods used. While the panel had concerns about the conflicting studies, there are other data suggesting some potential for TCE to cause CHD: chick embryo studies, the ability TCE metabolites to cause CHD. The ability of TCA to

cause cardiac effects should be discussed in the context of how much this metabolite would be formed after TCE administration

2. Another conflicting data set was seen with litter resorption as an endpoint. The Healy et al study used a dose level of 100ppm via the inhalation route and found an increase in the number of litters totally resorbed. In this study 2 animals died due to TCE overdose when the air supply malfunctioned, decreasing the confidence in the utility of this study. In contrast, an inhalation study conducted by Dow Chemical Company reported a potential increase in fetotoxicity at both 150 ppm and 600 ppm but the effect was not statistically significant and high levels of fetal resorption were evident in controls, again decreasing the confidence in the utility of this study.

3. For the calculation of air quality criteria for developmental effects the panel recommended use of the NTP Continuous Breeding study where TCE was administered in the diet. The LOEL in this study was 150 mg/kg/day for reproductive effects, but effects in the F1 generation were seen at the 75 mg/kg/day dose level and this is suggested as a LOEL for development. The difficulties inherent in a breeding study where both males and females are exposed are recognized. However, the dam can be modeled as a single unit and the possibilities of male mediated effects acknowledged.

4. In the brain demyelination study by Isaacson and Taylor, TCE was administered in drinking water during prebreeding, gestation, and lactation. This was viewed as an important study documenting the potential for TCE to cause neurodevelopmental toxicity. This study recognizes the importance of the inclusion of additional uncertainty factors for early development exposures.

- Recommendations

1. Scale appropriately for children (see CNS section)

2. In addition to the CHD derived criteria, it is recommended that the NTP continuous breeding study and neurological effects in offspring, fetal and early childhood exposures and uncertainty factors be used in the derivation of air quality criteria for developmental toxicity

4. **Potential criteria based on carcinogenic effects are derived from several studies in rats and mice using default and PBPK-based low-dose and cross-species extrapolations. Have the selection of studies, the application of extrapolation procedures (low-dose, cross-species) and the weight given the different risk estimates (liver, lung, kidney, lymphoma, testes) in the identification of recommended criteria based on carcinogenic effects been adequately justified?**

The Peer Review Panel members were impressed with the quality of the TCE cancer sections. In general, the document is focused, clearly written and it did an excellent job in identifying and critiquing key studies. Applications of PBPK models, dose-response methodologies and the use

of uncertainty factors were appropriate and based on mechanistic information when available. The importance of both oxidative and conjugative pathways were discussed in an organized and concise manner. However, panel members raised several issues for consideration or further emphasis by the New York State Department of Health (NYSDOH) and these are summarized in the following bullets:

- The fact that TCE is a multi-species and multi-site carcinogen with a combination of both malignant and benign tumors should be further emphasized in the document because these data coupled with the human data have led several authoritative bodies (EPA, NTP, & IARC) to the conclusion that TCE is on the cusp between a known and probable (likely, reasonably anticipated to be) human carcinogen. Thus, the NYSDOH should have flexibility in using risk levels of both 1 in 10^{-6} and 1 in 10^{-5}.

- One review detailed evidence in support of peroxisome proliferation as a MOA for mouse liver tumors and should be accorded less weight in the criteria document. Other panel members felt that the peroxisome proliferation evidence was suggestive but not sufficiently strong to rule out mouse liver tumors as an important data set in risk assessment because of knowledge gaps in the proposed mechanism and reports in the scientific literature that TCE exposure is associated with increased liver tumors in humans.

- Some panel members commented that NYSDOH should consider elevating the mouse lymphoma data to Tier 1 status. They noted that the data did not permit rejection of a positive dose response and that epidemiological studies have reported an association between NHL and TCE exposure. Evidence for this contention was detailed in one review and included reasons why meta analyses can mask important findings. Another panel member questioned the consistency of the association between TCE exposure and the incidence of NHL. In any event, the peer review panel agreed that site concordance between animal and human studies should not be a requirement for using animal studies in cancer risk assessments.

- Several panel members recommended that the NYSDOH organize the cancer tables according to tumor site in addition to organizing them by study.

- Panel members agreed that the NYSDOH had used PBPK models in an appropriate way for cross-species comparisons and dose response assessment. It is clear that humans metabolize TCE in a similar way as experimental animals. The panel also emphasized that while TCE metabolism is important to carcinogenesis, mechanistic information is limited and it is likely that different mechanisms are operative at different cancer sites. Panel members also recommended that the NYSDOH examine other data and models (in addition to Clewell) for deriving model parameters. This would help to describe the range of interindividual variations in metabolite formation and tumor responses. Interindividual variation is not considered in the linear portion of the analysis.

- The panel noted that non-linear extrapolation procedures, when used, did not include uncertainty factors for pharmacodynamics.

- Panel members commented that the NYSDOH did an excellent job in using benchmark dose procedures to establish the POD and for presenting results from both linear and non-linear extrapolation procedures. It was noted that available evidence is inadequate to justify using non-linear results in deriving the air criterion for cancer effects.

- The panel noted that kidney tumor data reported in human studies are exceptionally strong and that the evidence supports a genotoxic mechanism. Renal cell carcinomas from workers highly-exposed to TCE frequently contain a mutated tumor suppressor gene (VHL). This mutation was not present in the germline of diseased individuals nor in renal cell carcinomas from individuals not highly exposed to TCE. Also, a metabolite formed by the glutathione dependent pathway is mutagenic and it has been implicated in the formation of kidney tumors. These findings, taken together, provide strong evidence in support of linear dose response for kidney tumors. This supports consideration of a factor to account for early-in-life exposure following the EPA guideline (2005). These issues should be discussed further in the document.

- The NYSDOH should consider doing simulations with mixed mechanism assumptions (both linear and non-linear) as both mechanisms are likely involved in some tumor responses.

5. **The findings of increased risk for cancer in the Hansen, et al. (2001) study are used to check the plausibility of recommended carcinogenic criteria based on animal studies; earlier epidemiologic studies are not used to estimate risk. The human data are not used further in quantifying carcinogenic risks, although they are used in weight of evidence considerations. Is this decision adequately justified?**

   - The NYSDOH review does a good job of summarizing the existing epidemiology in a systematic and concise manner and fairly describes the strengths and weaknesses of the studies.

   - The rationale to utilize the human epidemiologic studies for weight of evidence support for the animal carcinogenicity studies rather than as the primary for the quantitative cancer risk assessment is appropriate. The weaknesses of the exposure estimates and potential confounding exposures support this decision. However, the DOH may want to consider the human studies to a greater extent when weighting the cancer evidence to establish a guideline.

   - Because the analyses are being used to support a TCE inhalation guideline, it is most appropriate to utilize the human epidemiologic studies which evaluate TCE inhalation

exposures. The Hansen et al (2001) study meets all the NYSDOH selection parameters and is a strong and appropriate choice. However, the Raaschou-Nielsen et al (2003) study and references therein have desirable attributes (large population and more exposure characterization) and including a more detailed analysis of this study along with Hansen would add perspective and would better reflect the richness in the many epidemiologic studies.

- Liver, kidney and non-Hodgkin's lymphoma are among the most consistent human cancer data and it would be beneficial to have a table summarizing the data from the various studies.

- Cancer risks are evaluated individually but the human experience is cumulative of all the risks. This should be mentioned and supports the need for a cautious approach to choosing the guideline.

- While concordance between animal and human sites is informative and useful, it should not be a limiting requirement for consideration of a cancer endpoint.

6. Is the summary transparent and does it adequately justify the guideline of 5 mcg/m^3?

- The use of scientific expert judgement in the evaluation and synthesis of scientific data is appropriate for establishing air guidelines. The basis for the determination of the final guideline of 5 $\mu g/m^3$ is not sufficiently clear and transparent. Show how you synthesize the data for a final decision regarding the recommended guideline value. The draft document should state clearly how these numbers were weighted and what justification was used in the final determination.

- Some panel members suggested that additional consideration be given to lowering the guideline value.

- Move the discussion of appendix A to the text and include in the discussion the differences between the DOH and EPA selection and use of studies for the development of an air guideline.

- Include aggregate and cumulative risks in the discussion. Include chemicals commonly found with TCE (ATSDR, EPA). Re-evaluate background levels of TCE in air. State how you will address exposure to chemical mixtures in evaluating risk.

- Childhood and *in utero* susceptibility needs to be explicitly addressed. Identify data gaps or strengths. DOH should consider using an UF of 3-10 to account for potential infant and childhood sensitivity in deriving potential air criteria based on both cancer and non-cancer endpoints.

We hope the New York State Department of Health finds these comments and suggestions useful. We look forward to the finalization of the TCE Air Criteria Document.

Sincerely,

Henry Anderson, M.D.

Trichloroethene (TCE) Peer Review Panel

Reviewer	Affiliation
Henry Anderson	Wisconsin Division of Public Health
J. Christopher Corton	Toxicogenomics Program US Environmental Protection Agency
George Daston	Miami Valley Laboratories Procter and Gamble Company
James Dix	Department of Chemistry State University of New York at Binghamton
Jeffrey Fisher	Department of Environmental Health Science University of Georgia
Peter Infante	School of Public Health George Washington University
Michael Kelsh	Exponent
Nathan Graber*	Center for Children's Health and the Environment Mount Sinai School of Medicine
George Lucier	National Institute of Environmental Health Sciences (retired)
Marion Miller	Department of Environmental Toxicology University of California at Davis
Daniel Wartenberg	Division of Environmental Epidemiology Robert Wood Johnson Medical School
Lauren Zeise	Office of Environmental Health Hazard Assessment California Environmental Protection Agency

*Philip Landrigan is the suggested reviewer, but will be represented by Nathan Graber.

Biographical Information

Henry Anderson, M.D. (Chair) is the State Environmental and Occupational Disease Epidemiologist and Chief Medical Officer for the Wisconsin Department of Health and Social Services. He is an Adjunct Professor in the Department of Preventive Medicine at the University of Wisconsin - Madison and the UW Institute for Environmental Studies, Center for Human Studies. He is President of the Council of State and Territorial Epidemiologists, is Chair of the Integrated Human Exposure Committee of the USEPA Science Advisory Board, serves on that board's Executive Committee and was a member of the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC). Dr. Anderson is a member of the Armed Forces Epidemiology Board and the CDC National Center for Environmental Health, Directors Advisory Committee. He is a fellow of the Collegium Ramazzini and the American Association for the Advancement of Science.

Chris Corton, Ph.D. is a Senior Research Biologist and Leader of the Toxicogenomics Program in the Division of Environmental Carcinogenesis, National Health and Environmental Effects Research Laboratory (NHEERL) at the US-EPA in Research Triangle Park, North Carolina. He received his Ph.D. in biochemistry at the University of Kansas Medical Center. He received training as a post-doctoral research fellow at Duke University. He is an adjunct faculty member at the University of North Carolina, Chapel Hill and University of Louisiana, Monroe. Dr. Corton serves on numerous ad hoc review panels for NIH and NCI. He currently serves on the editorial boards for Toxicological Sciences, Toxicology Letters and Chemico-Biological Interactions.

George Daston, Ph.D. is a Research Fellow at Procter & Gamble's Miami Valley Laboratories. His research is in the areas of developmental toxicology and risk assessment. Dr. Daston's professional activities include serving as President (1994-95) of the Society of Toxicology's Reproductive and Developmental Toxicology Specialty Section; President (1999-2000) of the Teratology Society; member of the National Academy of Sciences Board on Environmental Studies and Toxicology (1995-98); Councilor of the Society of Toxicology (2001-2003); member of the EPA Board of Scientific Counselors; member of the US National Toxicology Program Board of Scientific Counselors; and member of EPA's Endocrine Disrupter Screening and Testing Advisory Committee (EDSTAC). Dr. Daston is Editor-in-Chief of Birth Defects Research: Developmental and Reproductive Toxicology, and is an Adjunct Professor in the Department of Pediatrics and Developmental Biology Program at the University of Cincinnati and Children's Hospital Research Foundation. Dr. Daston was a Visiting Scientist at the Salk Institute, Molecular Neurobiology Laboratory, 1993-94. Dr. Daston was elected a Fellow of AAAS in 1999.

James Dix, Ph.D. is Associate Professor of Chemistry at the State University of New York, Binghamton. He obtained his BA in Chemistry at Grinnell College and Ph.D. in Physical Chemistry at UCLA, and did post-doctoral work in biophysics at Harvard Medical School. He has served as Visiting Scientist in the Cardiovascular Research Institute, University of California, San Francisco, and in the Theoretical Biology and Biophysics Group at Los Alamos National Laboratory. His research interests are in experimental and computational approaches to study molecular motion in biological systems, and in science education. His research has been

supported by the National Science Foundation, the National Institutes of Health, and private corporations. He is a member of Residents Action Group of Endicott.

Jeffrey Fisher, Ph.D. is a Professor and Department Head of the Department of Environmental Health Science, College of Public Health at the University of Georgia. Dr. Fisher's research interests are in the development and application of biologically based mathematical models to ascertain health risks from environmental and occupational chemical exposures. He spent most of his career at the Toxicology Laboratory, Wright Patterson AFB. Dr. Fisher's modeling experience includes working with solvents, PCBs and perchlorate. He had developed models for cancer risk assessment, estimating lactational transfer of solvents, understanding in utero and neonatal dosimetry, quantifying metabolism of solvent mixtures and for inhibition of thyroidal uptake of radioiodide. Dr. Fisher has 18 years of experience in physiological modeling and has trained graduate students and postdoctoral fellows on the concepts and application of physiological models. He has served on several federal panels and advisory boards, and worked with NATO countries. He is a member of the National Academy of Sciences Acute Exposure Guideline Levels (AEGL) subcommittee. He was a visiting scientist at CIIT Centers for Health Research and NIOSH. Dr. Fisher has over 75 publications.

Nathan Graber, M.D. is a pediatrician currently training in the Pediatric Environmental Health Fellowship Program established by the Ambulatory Pediatric Association at the Mount Sinai School of Medicine. In 2000, he graduated from The Sackler School of Medicine in Tel Aviv, Israel. Returning to the Bronx, he completed his residency in Pediatrics at Jacobi Medical Center of the Albert Einstein College of Medicine. While training in his current fellowship he is completing a Master of Public Health. His area of focus has been lead exposure during pregnancy and has been involved in projects investigating the epidemiology, risk factors and clinical implications of this important public health problem. He is currently a member of the CDC Workgroup on Lead in Pregnancy and the New York City Department of Health Workgroup to promote screening of children for lead poisoning. He is Co-Chair of the Pediatric/Child Health Subcommittee of the East Harlem Community Health Committee. In addition to caring for his general pediatric patients, he staffs the Mount Sinai Pediatric Environmental Health Specialty Unit and a busy Pediatric Emergency Room in the Bronx.

Peter F. Infante, D.D.S., Dr.P.H. is an Adjunct Professor of Environmental and Occupational Health, George Washington University School of Public Health and Health Services. He has a Doctor of Public Health degree from the Department of Epidemiology, University of Michigan. He is a Fellow of the American College of Epidemiology and of the Collegium Ramazzini. For 27 years, he conducted research into the cancer causing effects of toxic substances found in the workplace and also regulated a number of these substances while at the US Department of Labor, Occupational Safety and Health Administration. He has served on numerous national and international panels and working groups related to the identification of causes of human cancers, including the International Agency for Research on Cancer, the National Cancer Institute (NCI), the President's Cancer Panel, the Office of Technology Assessment of the US Congress, and the National Academy of Sciences Committee on Toxicology. He has testified before regulatory bodies in both the US and Canada and several times before the US Congress on matters of industrial pollution. He was selected as one of only four experts world-wide to testify before the World Trade Organization as part of its deliberations on the banning of asbestos containing

products from the all of the European Union countries in 2000. He is the author of more than 100 peer-reviewed articles on the subject of occupation and cancer.

Michael A. Kelsh, Ph.D., M.P.H. is a Principal Scientist in Exponent's Health Sciences practice. Dr. Kelsh is an Adjunct Professor at the UCLA School of Public Health and teaches seminars in occupational epidemiology and exposure assessment. Prior to joining Exponent, he was the Director of Occupational and Environmental Health Applications and a Senior Epidemiologist at EcoAnalysis Inc. He specializes in the application of epidemiology and biostatistics to occupational and environmental health issues. Dr. Kelsh has conducted epidemiologic studies of occupational injuries, musculoskeletal diseases, respiratory and neurological diseases, and cancer incidence and mortality. Dr. Kelsh has a background in exposure assessment studies with emphasis on electric and magnetic fields exposures and workplace ergonomic factors.

George Lucier, Ph.D. is a consultant in toxicology. He is a Senior Adjunct scientist for Environmental Defense, an advisor to the National Institutes of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP), and a member of EPA's Science Advisory Board. He retired from the NIEHS in 2000 where he was Director of the Environmental Toxicology Program, Associate Director of the NTP and head of a research group in molecular epidemiology and dosimetry. In his NTP role, Dr. Lucier was responsible for coordinating toxicological research and testing across Federal agencies including EPA, FDA and NIOSH. His research focused on the use of basic biology to reduce uncertainty in human risk assessments and to improve the tools used in exposure assessment. Dr. Lucier was editor of Environmental Health Perspectives for 28 years where he is still a consulting editor. He received his Ph.D. from the University of Maryland School of Agriculture.

Marion Miller, Ph.D. is a Professor in the Department of Environmental Toxicology, University of California, Davis. Her research interests are in the areas of reproductive toxicology, metabolism and pharmacokinetics. She is Associate Director of the UC Systemwide Toxic Substances Research and Teaching Program, and Director of the Western Region IR-4 Project (USDA), a national agricultural program to clear pest control agents for minor use crops. Dr. Miller has served as a member (1994-2004) and as chair (2002-3) of the Science Advisory Board for OEHHA (Office of Environmental Health Hazard Assessment), Cal/EPA, Developmental and Reproductive Toxicant (DART) Identification Committee for the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). She is a member of the Society of Toxicology and has served on the SOT K-12 Education subcommittee.

Daniel Wartenberg, Ph.D. is Professor and Director of the Division of Environmental Epidemiology in the Department of Environmental and Occupational Medicine at the Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey (UMDNJ), and Professor in the Division of Epidemiology in the UMDNJ School of Public Health. He was a Libra Scholar in the Department of Applied Medical Sciences at the University of Southern Maine in 2005, is a Fellow of the American College of Epidemiology, is President-Elect of the International Society of Environmental Epidemiology, is a member of the Board of Scientific Counselors for the National Center for Environmental Health/Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention and has served on a variety of

other scientific advisory committees for local, state, national and international groups. Dr. Wartenberg's main research interest is the development and application of novel approaches to the study of environmental risk, pollution, and public health, with particular emphasis on geographic variation, disease clustering and the application of Geographic Information Systems (GIS).

Lauren Zeise, Ph.D. is Chief of the Reproductive and Cancer Hazard Assessment Branch of the California Environmental Protection Agency. She received her Ph.D. from Harvard University. Dr. Zeise's research focuses on modeling human interindividual variability and risk. She has served on advisory boards of the EPA, WHO, OTA, and NIEHS. She has also served on several NRC committees, including the Committee on Risk Characterization, the Committee on Comparative Toxicology of Naturally Occurring Carcinogens, the Committee on Copper in Drinking Water, and the Committee to Review EPA's Research Grants Program. Dr. Zeise is currently a member of the Board on Environmental Studies and Toxicology and the Institute of Medicine (IOM) Health Promotion and Disease Prevention Board.

Trichloroethene Peer Review Panel

CHARGE

The panel is being asked to review and comment on NYS Department of Health's Trichloroethene (TCE) Air Criteria Document. Any comments are welcome. We are particularly interested in receiving comments on the following areas:

- the adequacy of the analysis and conclusions of the risk assessment;
- the selection of principal studies, critical endpoints, uncertainty factors for non-carcinogenic and carcinogenic effects, and methods for calculating risk, both non-carcinogenic and carcinogenic;
- dose-response and physiologically-based pharmacokinetic (PBPK) modeling and
- critical information that is not discussed.

We are asking for written responses to the following questions.

Specific Questions

1. Does the discussion on animal and human central nervous system effects adequately justify development of the recommended criterion based on those effects?
   (Anderson, Corton, Dix*, Kelsh)

2. The data from Land et al. (1981) and DuTeaux et al. (2004) (inhalation and drinking water studies, respectively) are used to develop potential criteria for reproductive effects. Does the discussion adequately justify recommended criterion based on reproductive effects?
   (Daston, Graber, Miller, Zeise*)

3. The Dawson et al. (1993 data) are used together with other information provided by the study authors to develop potential criteria based on developmental effects. Does the discussion adequately justify the recommended criterion based on developmental effects?
   (Daston, Infante, Miller*, Zeise)

4. Potential criteria based on carcinogenic effects are derived from several studies in rats and mice using default and PBPK-based low-dose and cross-species extrapolations. Have the selection of studies, the application of extrapolation procedures (low-dose, cross-species) and the weight given the different risk estimates (liver, lung, kidney, lymphoma, testes) in the identification of recommended criteria based on carcinogenic effects been adequately justified?
   (Corton, Fisher, Lucier*, Wartenberg)

5. The findings of increased risk for cancer in the Hansen, et al. (2001) study are used to check the plausibility of recommended carcinogenic criteria based on animal studies; earlier epidemiologic studies are not used to estimate risk. The human data are not used further in quantifying carcinogenic risks, although they are used in weight of evidence considerations. Is this decision adequately justified? (Anderson*, Infante, Kelsh, Wartenberg)

6. Is the summary transparent and does it adequately justify the guideline of 5 mcg/m3? (Dix, Fisher*, Graber, Lucier)

Health Statistics Review

Questions

1. Does this health statistics review affect the discussion/conclusions about trichloroethene's toxicity in the criteria document in a substantive manner?

2. Do you have any comments or suggestions about follow-up activities, including those we are recommending?

* Lead for Coordinating Responses

Attachment C

TRICHLOROETHENE PANEL MEETING AGENDA
THE DESMOND HOTEL & CONFERENCE CENTER

AUGUST 29-30, 2005

Day One

8:30 – 9:00	Coffee/Continental Breakfast	
9:00 – 9:15	Introduction, Charge, Disclosure	Nancy Kim
9:15 – 9:30	Non-Cancer Endpoints – Overview	DOH Staff
9:30 –10:30	Discussion of Central Nervous System Effects – Question 1	
10:30 – 10:45	Break	
10:45 – 12:00	Discussion of Male Reproductive Effects – Question 2	
12:00 – 1:00	Lunch	
1:00 – 2:30	Discussion of Developmental Effects – Question 3	
2:30 – 2:45	Break	
2:45 – 3:00	Cancer Endpoints – Overview	DOH Staff
3:00 – 4:30	Discussion of Cancer Endpoints – Question 4 and 5	
4:30 – 5:00	Public Comment Period	

Day Two

8:00 – 8:30	Continental Breakfast	
8:30 – 8:45	Criteria and Health Statistics Overview	DOH Staff
8:45 – 10:00	Discussion of Transparency and Justification of Guideline – Question 6	
10:00 – 10:30	Discussion of Health Statistics Review – Questions	
10:30 – 10:45	Break	
10:45 – 12:15	Review Draft Responses to Questions	
12:15 – 1:30	Lunch, Revise Responses	
1:30 – 2:30	Other Comments	
2:30 – 3:00	Next Steps, Adjourn	Nancy Kim

TRICHLOROETHENE PEER REVIEW PANEL
INDIVIDUAL RESPONSE TO QUESTIONS

General

- Reviewer

The Air Criteria Document does a good job of reviewing the available scientific published literature in an organized and systematic fashion. At times the use the term criteria or criterion it is a bit confusing. It is used to represent the endpoint of the process (as in the Air Criteria) or the end guideline used to characterize a health endpoint, rather than the means used to assess a study or to describe the process applied during the evaluation of studies. While the studies chosen as the key study for each endpoint appear reasonable, it is not fully transparent as to what "criteria" were applied by NYSDOH to determine the quality of studies and determine which were the strongest. While it is usually mentioned that the Air Criterion was usually chosen from the most protective end of the calculated ranges of NOELs or LOELs, it was not clear where the quality of the study was factored in or how. If the lower end of the range of "equal quality studies" was a "criteria" then that should be stated. In other words it would be helpful in the introduction to describe how the many available studies were evaluated, what was looked for and how they were determined to be valid etc. Each study is nicely summarized, but the standard quality of the science should be mentioned.

One small thing, it would be useful to the out-of-state reader to have the introduction describe the statutory authority etc under which the criteria is developed as well as how the document and the chapters are organized. Some brief discussion of the earlier 2003 Air Criteria would be helpful as background. Does this document follow the process used in 2003 with newer studies and the PBPK and MOE advances added in? Or is this the end of a process that began with the 2003 recommended guideline?

It becomes apparent as the document is read that each section begins with a discussion of the human data, then animal data then the potential Air Criteria including a discussion of the critical study and mode of action if appropriate. It is a good logical format, but it would help if the introduction set the stage a bit better.

It would also be helpful if in the introduction were a brief discussion of how children's issues are addressed. The adjustment for weight and surface area etc used is fine, but there is no discussion if children are more susceptible to some of the health effects than others and if the intra-species uncertainty factor is being used to account for such vulnerability.

- Reviewer

While I applaud the use of benchmark methodology, there was not sufficient information in the criteria document for me to determine whether the method was being appropriately used. Many of the endpoints being modeled are continuous variables, for which there are a number of possible choices of a 10% or 5% effect level. The choices made, and the rationales, need to be given. One choice that is not acceptable is to simply choose a 10% increase (or decrease) in a continuous variable, as this may have no relevance. For example, a 10% increase in blood urea nitrogen over control (say, from a value of 20 to 22) would not be statistically or biologically significant. The right choice should consider the variability of the measurement (e.g., 0.5 SD, 1 SEM) or should be a value at or above a criterion value for abnormal (e.g., outside the range identified by clinical chemists as normal, for the BUN example).

1. **Does the discussion on animal and human central nervous system effects adequately justify development of the recommended criterion based on those effects?**

- Reviewer

There is no question that CNS effects are important in understanding TCE toxicity and that there is considerable literature describing such effects in humans as well as different laboratory animal species. The issue is more one of how to measure the effect and the exposures that cause them and through what mechanism. There is no clear common NOEL. But there is ample information upon which to base the development of a reliable CNS criterion. The LOELs identified are appropriately based on the data in each of the studies. While I would agree that the Rasmussen et al (1993) study is the strongest human study of neurological effects, I am not sure I made my decision based upon the same criteria as NYSDOH. It would be helpful if the NYSDOH would indicate why they felt it was the strongest study. What "criteria" were used to make that assessment? The cancer section does a good job of describing how the studies were evaluated and used a published set of assessment parameters. Was the CNS a quantitative process or qualitative? Such a discussion would help with transparency of the decision making process. Were the Briving et al (1986) animal study and the Arito et al. (1994) considered equally robust? Mention is made that Arito was chosen because it had the lower adjusted LOEL. The quality of the studies ought to have entered in as well.

The discussion of the derivation and use of uncertainty factors was clear and gave a concise rationale for each. The mode of action and dose metrics discussion was clear. The listing of the uncertainties / limitations / strengths is mostly uncertainties and limitations. It would be useful to also mention the strengths of the studies chosen and the concordance of the data. Compared to what is often available for risk assessment there is a wealth of information on TCE and that should be stressed.

- Reviewer

The selection of the critical studies appears to be appropriate. The Arito et al. study describes the effects of TCE inhalation on a number of parameters that are arguably associated with cns effects. The most important endpoint which significantly impacts the risk assessment is wakefulness which could be determined by a number of factors. However, the use of this endpoint is strengthened by the fact that humans exposed to TCE experience drowsiness as stated in the document.

The main concern in this section is the departure from an uncertainty factor of 10 for the extrapolation of LOEL to NOEL. There is inadequate information to support this factor based on the studies cited in the text and the Arito study itself.

Although Storm and Rozman (1998) reviewed a number of studies in animals and humans and found that the ratio ranges from 1.5 to 5, these ratios are highly dependent on the selection of the endpoint as well as the doses in the study. There is no indication from this analysis that the primary endpoint that is used in the risk assessment (i.e., decreased wakefulness) is included in the endpoints evaluated. Importantly, in the primary data presented in the Arito et al. study, there is little indication that there is a trend toward decreasing responsiveness at the lowest exposure of 50 ppm. In fact, all of the exposures appear to induce the response to the same extent and have the same p value of 0.01. Thus, there does not appear that there is an indication that at 3-fold less exposure levels the response will be nonsignificant. It should be noted that the use of an uncertainty factor of 10 in place of 3 will not change the recommended TCE guideline of 5mcg/m3.

The selection of the other uncertainty factors appears to be justified.

- Reviewer

It is clear that TCE affects the central nervous system; the unknown is the concentration below which there is no effect. The NYS DOH draft report sets this concentration at 40 $\mu g/m^3$.

The critical animal study selected for CNS toxicity is Arito et al. (1994). Of the animal studies cited in Table 3-1 of the NYS DOH draft document, Arito is the appropriate critical study based on the study method (direct brain electrical measurements) and design. This study was also used by ATSDR (1997) in setting a minimal risk level of 0.1 mg/kg da, cited by the EPA (2001) as supporting their TCE RfC, and used by Barton and Clewell (2000) in their discussion of risk assessment. Effects on CNS in rats were found at a lowest concentration of 50 ppmv (269 mg TCE/m^3).

Of the human studies, Rasmussen et al (1993) is the critical study. Unfortunately, the Rasmussen study is not precise enough to be used in setting a quantitative LOEL or NOEL, and the draft study is correct in relegating this study to the status of supporting documentation.

The conversion from 269 mg TCE/m^3 to an equivalent exposure in humans seems to be missing a correction factor for the differing body masses and lung capacities of humans and rats. It is not clear why this factor has been omitted; it was included in the ATSDR calculation. Using the factors (70 kg human)/(0.2 kg rat) and (0.2 m^3 rat/da)/(20 m^3 human/da) increases the human equivalent LOEL by a factor of 3.5.

The NYS DOH is to be commended for extending the TCE air criterion to potentially susceptible populations such as children. However, the lower guideline for children was not put in the Executive Summary. How does DOH intend to use the lower guideline for children? Since much of the inhalation exposure is via vapor intrusion into homes that are likely to house children, it

appears that the children guideline would be the appropriate one to promulgate. Also, the Executive Summary states that "These criteria range from 40 to 519 micrograms per cubic meter of air," referring to the study of Arito et al. This appears to be misleading, since the Arito et al. study leads to criteria of 64 (adult) or 26 (child) $\mu g/m^3$ (adult). The Executive Summary should clearly state those criteria.

The mode of action of TCE on the CNS is not known, but the draft report makes a good case for the involvement of TCOH.

Four uncertainty factors are used. The interspecies factor of 3, intraspecies factor of 10, and sub-chronic to chronic factor of 10 are standard and well justified. The lowering of the standard uncertainty factor for LOEL/NOEL from 10 to 3 is not clear. The argument made in the draft report is that in three studies and a review, there is evidence that the TCE NOEL is more than 1/10 the LOEL, and therefore a factor of 3 "should be sufficient." If there really is a TCE NOEL, then why not use the NOEL instead of the LOEL from Arito et al.? Also, the measurement device used for the effect might be not sensitive (anesthetic properties in one case, neurobehavioral tests in another, discrimination task performance in another) to pick up an effect. All told, the reduction of 10 to 3 for the LOEL/NOEL is not well justified.

2. **The data from Land et al. (1981) and DuTeaux et al. (2004) (inhalation and drinking water studies, respectively) are used to develop potential criteria for reproductive effects. Does the discussion adequately justify recommended criterion based on reproductive effects?**

- Reviewer

Neither the Land nor the DuTeaux paper should be used as the critical study for establishing a criterion for reproductive effects. DuTeaux et al., although a very nicely executed investigative toxicology study, used too few animals for the study to be used as support for a risk assessment. Only 3 animals per group were used in the study; in some instances, samples could only be analyzed for two of the three animals per group (e.g., sperm motility, sperm concentration). Furthermore, the animals in each group were not well matched in weight: the mean starting weight in the 0.4% TCE group was 10% higher than the mean starting weight of the controls. While this difference was not statistically significant, the lack of significance is attributable to the lack of statistical power for such a small sample size. Had the study involved 10 rats per group, the difference in starting weights would have been significant. Given the pharmacokinetic behavior of TCE, this difference in body weights among the experimental groups is not trivial, as it is likely to be accompanied by differences in body fat percent.

The real value of the DuTeaux study is that it indicates a possible target site for TCE toxicity, the efferent ductules. It also provides a possible explanation for why this is a target, and why sperm quality may be affected in the absence of measurable effects on sperm production. As such, it is an important supporting study, but should not be used as the support for a criterion value.

The Land et al. study appears to be more useful for risk assessment, but has some limitations that make it a less-than-optimal choice as the critical study. (Note: I was only able to obtain an abstract from PubMed, and could not view a copy of the entire paper.) The dosing regimen was limited (five days of exposure), which has necessitated the use of an additional uncertainty factor. Only two dose levels, an order of magnitude apart, were used, making it difficult to determine dose-response characteristics. I did not find any information about the number of animals used per group, but given that the study was a survey of the toxicity of eight compounds, it is likely that the number was small. Finally, in 1981 the science of assessing rodent sperm morphology was in its infancy; it is possible that some of the morphological changes reported are now being interpreted as variations, not abnormalities.

I recommend that the NTP continuous breeding study be used as the critical study for risk assessment. It used multiple dose levels, a protocol with good sensitivity and statistical power, and evaluated endpoints that are directly

relevant for assessing reproductive function and outcome. The study has been reviewed by experts within and outside NTP, who concur on a NOAEL, 75 mg/kg/day. This would translate into an atmospheric concentration in the 250 ug/m3 range, not inconsistent with the points of departure derived from the DuTeaux and Land studies, but much more scientifically supportable. Fewer uncertainty factors, and of lesser magnitude, need to be applied to this point of departure. There is no need for a LOAEL-to-NOAEL conversion; the 10x factor to account for chronic exposure can either be reduced or eliminated.

3. **The Dawson et al. (1993 data) are used together with other information provided by the study authors to develop potential criteria based on developmental effects. Does the discussion adequately justify the recommended criterion based on developmental effects?**

- Reviewer

I do not agree that the Dawson paper should be used as the critical paper for developmental effects. No other investigators have reported similar effects from TCE. This includes a study by Fisher et al. (2001) that replicated the examination methods used by Dawson and Johnson. The database also includes a number of studies that were more statistically robust than the Dawson/Johnson studies, and which conform to internationally accepted regulatory guidelines for developmental toxicity studies.

The arguments put forth in the criteria document to accept the Dawson results over the Fisher results (page 85, second paragraph) are not convincing. The document suggests that the high background rate of malformations in the controls in Fisher's study may have diminished the ability to detect a TCE-induced increase. It seems more likely to me that the high background rate is an indication that the observation method being used is hypersensitive, and that trivial changes are being recorded as abnormalities
. In fact, one could interpret the results of the Johnson et al (2003) study as supporting this notion that the assessment technique produces a lot of false positives, in that there is essentially no slope to the dose-response curve over four orders of magnitude (0.25 ppm-1100 ppm). (It should also be noted that the dose-response study had no concurrent controls; therefore, it is impossible to know whether the values in the treated groups are elevated.)

The document also argues that Sprague Dawley rats sourced from Charles River may have responded differently than Harlan-sourced SD rats. I think this is unlikely, although not impossible. However, given that none of the other well-conducted studies over the years have reported similar effects, despite the fact that different strains and suppliers were probably used and that genetic drift has occurred, makes me think the possibility is small. The document also suggests that gavage dosing (Fisher) would have produced different results from drinking water. I find this unlikely, as the gavage dosing would have resulted in a higher peak concentration. The argument that exposures on gestation days 6-18 may have been less effective than dosing throughout pregnancy is also not credible, in that the kinetics of TCE are such that this should not make a difference in systemic load, and because the critical period for heart development in the rat embryo begins on gestation day 8 or 9.

In sum, the collection of papers from the Dawson/Johnson lab appear to be the outliers in a data set that is robust. The rest of the data set indicates that

developmental toxicity is observed only when maternal toxicity is marked. No other studies report cardiac malformations.

The criteria document discusses the possibility that the fetal cardiac evaluation method used in most developmental toxicity studies is not sensitive enough to detect cardiac malformations. This is not the case. There are numerous reports in the literature in which cardiac teratogens have been detected using the methods employed in guideline studies. The historical database on background malformation rates kept by the Middle Atlantic Reproduction and Teratology Assoc. (MARTA), lists cardiac and great vessel malformations, all of which were detected using the traditional dissection methods. I also spoke with Ed Carney, who was cited in the criteria document and who was involved in the TCE developmental toxicity study conducted at Dow Chemical. Dr. Carney indicated to me that he had seen the Dawson/Johnson method of evaluation demonstrated to him (by the scientists at Wright-Patterson AFB who tried to replicate the Dawson study) and that in his opinion the only feature of cardiac anatomy that could be visualized better by that method was the movement of the valves. It was his opinion that septal defects would be detected by the traditional methods of fetal soft tissue evaluation.

My recommendation is that the Dow inhalation study is the optimal choice to serve as the critical study for risk assessment. It is conducted according to internationally accepted guidelines, by a lab working under GLP conditions. The criteria document indicates that the results are consistent with other results from the literature.

4. **Potential criteria based on carcinogenic effects are derived from several studies in rats and mice using default and PBPK-based low-dose and cross-species extrapolations. Have the selection of studies, the application of extrapolation procedures (low-dose, cross-species) and the weight given the different risk estimates (liver, lung, kidney, lymphoma, testes) in the identification of recommended criteria based on carcinogenic effects been adequately justified?**

- Reviewer

PBPK modeling and cancer risk estimates for liver, lung, kidney, lymphoma, and testes. You arrived at the place you need to be with the type of cancers, but the text is worded such that it overstates what is really known. A good rationale is needed for use of linear dose model for liver cancer using TCA as the dosimetric (epigenetic vs. genetic).

PBPK modeling: I am enthused to see the use of the models for estimating dosimetry for use in risk assessment. Congratulations! Since I have spent 15 years conducting TCE/metabolite experiments to support model development and validation in laboratory animals and humans I could write pages on the topic. I will make a few conceptual comments to strengthen the scientific basis for use of the PBPK models in this process.

You should know....the US EPA states that a bias exists in the use of the models because all the models are developed based on the work of me and my colleagues with some extensions of the models provided by others, such as Clewell and Simon. This should still be on their web site. ...A sore spot for me.

Perhaps, the most perplexing issue about TCE is that the MOA or mechanisms of action are not well established despite years of research. This raises concerns about assuming equivalent risk (eg., dosimetry models are conservative for cancer) when extrapolating internal dose from lab animals to humans. Also the selection of dosimetrics can be important and questioned relative to the proposed MOA. This could be the case for some of your endpoints other than liver.

In laboratory animals (mice) the best documented target organ is the liver. Studies have been carried out with TCE and several metabolites (chloral hydrate, TCA, DCA) to show that liver cancer occurs when each is administered. There is a smoking gun for the mouse in terms of responsible metabolites. For humans, liver cancer is questionable based on PPAR alpha and peroxisome proliferation. I do not think there are any more smoking guns for TCE and cancer.

The use of PBPK models to assign risk to target tissues other than the liver should be completed under the framework of protecting the public health (eg., not

science) or for hypothesis generation. For example, the use of the PBPK models to address kidney cancer using DCVC is not recommended because of an almost complete lack of kinetic/metabolic experimental data to support this pathway. Furthermore, DCVC has not been shown to cause kidney cancer, in the same way chloral hydrate, TCA or DCA has been shown to cause cancer in the liver. Another metabolic pathway for kidney cancer has been proposed by Dr. Green. The use of the PBPK model to predict dosimetrics for other cancers such as lymphomas and cancer of testes can be questioned in the same fashion.

Without using the dosimetric, total amount metabolized, a risk conservative approach might be to assign the TCA (free fraction) as an internal dose 'surrogate' because it is the longest half life in the body. The use of TCE itself as a dosimetric seems advisable only when predicting CNS effects or perhaps portal of entry effects, even lung cancer. The lung cancer idea about build-up of chloral hydrate is ok, but it is just a hypothesis. There is quite a bit of chloral hydrate circulating in blood after exposure to TCE (in mice but not humans) and the distinction between hepatic- and clara cell- produced chloral hydrate was never addressed sufficiently.

I do not propose going back to administered dose of TCE, but the modeling work of Harvey Clewell et al showing risks for various pathways will not bear out under scientific scrutiny, such as the harmonized modeling effort that was conducted or perhaps in the ongoing NAS subcommittee. The modeling efforts of the US EPA with the harmonized model may keep various metabolic pathways in the model but I doubt that they will rely on its predictions since it represents primarily hypothesis generation. *Perhaps, NYS should qualify some of its risk predictions by not giving equal weight to each.* You do this in Table 5-26, but the text should be reworded to reflect this concern.

It would be nice if a chapter was added for the PBPK models. Include the model parameter values along with a few simulations of kinetic data to show that the models reproduce some of the data adequately. One important emerging practical aspect of Bayesian analysis is that the new fitted model parameter values may times falls outside of the range of the empirically determined or fitted values (deterministic) causing concern over the validity of the model parameter. This is especially problematic when the model parameter value is closely tied to the risk prediction. It would be very useful to provide a table with the experimentally determined and/or starting values for the model parameters and cite their origin and the final Bayesian determined value. You can get a better fit to the data by doing the large scale fitting exercise but the biological basis for the parameter may not be plausible or even worse the fitted key parameters 'affect' the risk predictions.

I was unclear how the free TCA was used. It seems ok in the Tables. Clewell and Andersen (2004) did not appropriately use our experimental findings for the mice, rat and human TCA binding information. The Keys et al. poster and the

Lumpkin et al. paper provide the correct information. The % of TCA bound in whole blood is constant across a wide range of blood levels and goes up at low doses and down at very high doses.

Using only the Clewell et al. PBPK model leaves out several important more recent kinetic data sets in human and as I recall mice. Please check on this.

Greenberg, M. S., G. A. Burton, Jr., and J. W. Fisher. 1999. Physiologically Based Pharmacokinetic Modeling of Inhaled Trichloroethylene and its Oxidative Metabolites in B6C3F1 mice. Toxicology and Applied Pharmacology 154, 264-278.

Abbas, R. and J. W. Fisher. 1997. A Physiologically Based Pharmacokinetic Model for Trichloroethylene and its Metabolites, Chloral Hydrate, Trichloroacetate, Dichloroacetate, Trichloroethanol, and Trichloroethanol Glucuronide in B6C3F1 mice. Toxicol. Appl. Pharmacol. 147, 15-30.

Fisher, J. W., D. Mahle and R. Abbas. 1998. A Human Physiologically Based Pharmacokinetic Model for Trichloroethylene and its Metabolites, Trichloroacetic Acid and Free Trichloroethanol.
Toxicology and Applied Pharmacology 152, 339-359.

Also, for the sake of keeping up to date, the short communication below gives new preliminary data on metabolically formed DCA. I think excluding DCA is the only way to go at this time because of issues that you are aware of.

Delinsky, A.D., D.C. Delinsky, S. Muralidhara, J.W. Fisher, J.V. Bruckner, and M.G. Bartlett. 2005. Analysis of dichloroacetic acid in rat blood and tissues by hydrophilic interaction liquid chromatography by hydrophilic interaction liquid chromatography with tandem mass spectrometry. Rapid Communications in Mass Spectrometry, 19, 1075-1083.

- Reviewer

The short answer to this question is yes. The document does an excellent job in describing the strengths and weaknesses in cancer studies in animals and humans. Greater weight is accorded to those sites where there is consistency across studies, biological plausibility, reasonable dose response relationships and animal/human concordance. Thus, the document relies on cancer effects on the liver/biliary system, kidney, esophagous as well as NHL. The NYDOH evaluation is, for the most part, consistent with evaluations made by the EPA and NTP which conclude that the animal cancer data is convincing but the human data may fall just short of the evidence needed to justify the highest cancer rating. All key studies have been identified.

The metabolism/mechanism issues are dealt with completely and objectively. The role of metabolism is discussed as well as the evidence in support of the conclusion that TCE metabolites are playing a key role in the carcinogenic actions of TCE including the evidence of genetic toxicity and effects on cell proliferation. The sections on P-450-dependent and glutathione transferase pathways are clearly written and help in assessing the use of PBPK models in deriving dose response relationships including the application of benchmark dose methodologies. These approaches are consistent with recommendations made by EPA in their revised cancer risk assessment guidelines.

The NYDOH appropriately concludes that available evidence is insufficient to move away from a linear dose response model although some additional details may be helpful here. For, example the fact that TCE is a multi-site carcinogen in animals and probably in humans as well means that arguments that question a linear dose response must be presented for all sites not just one or two. Clearly, this has not been done and the arguments in favor of a non linear dose response at any site are inadequate, at this point, to move away from linear extrapolation models.

5. **The findings of increased risk for cancer in the Hansen, et al. (2001) study are used to check the plausibility of recommended carcinogenic criteria based on animal studies; earlier epidemiologic studies are not used to estimate risk. The human data are not used further in quantifying carcinogenic risks, although they are used in weight of evidence considerations. Is this decision adequately justified?**

- Reviewer

There are many ways the cancer risk from TCE can be evaluated. It is clear that divergent methods have been used by different groups and governments. There is no one "best" process. Although there is a substantial set of human epidemiological studies, the NYSBOH review fairly describes the controversy that has surrounded the assessment of the human exposure experience and the diversity that is seen in the different study results.

It is reasonable to use the approach described and the rationale is appropriately documented. The animal data is less equivocal than the human and provides less variability. But the two sets of information are nicely linked and give confidence that the Criterion selected is adequately protective for the general population. The cancer section does a good job of describing how the human and animal studies were evaluated. The set of assessment parameters from the published literature is helpful in understanding how priorities were set. This section was very helpful in understanding the rationale for the approach

.

The issue of tumor site concordance between human epidemiology and the animal studies has considerable appeal; however the laboratory animal models are not designed to reflect specific human cancers, but rather for the broader issue of carcinogenicity. Of greater importance is whether the MOA resulting in the tumor is understood and is also active in humans. Such a MOA is discussed under the kidney cancer review. Tumors seen in animals may not be significantly increased in humans because of multiple contributing causes to the cancer in humans, age relationships and a myriad of confounders not present in the animal models. So while interesting to note, cancer site concordance should not be given undo weight.

The section does a nice job of summarizing a complex set of studies and issues and carefully describes the decision process used. The approach used is a reasonable one.

- Reviewer

The NYDOH review relies primarily on Wartenberg et al., 2000 review of epidemiologic studies of TCE exposed and a review of recent studies published after 2000 to conclude (pg 128) "Collectively, the analyses presented in

Wartenberg et al and additional data presented in subsequent publications on the effects of occupational exposures ...provide evidence for an association between occupational TCE exposure and several types of cancer in humans most notably renal cell carcinoma, NHL, liver/biliary cancer, esophageal adenocarcinoma, and to a lesser extent Hodgkin's disease and cervical cancer."

The NYDOH review acknowledges differences in scientific opinion on this issue (e.g. Wong 2004, Institute of Medicine 2003, and Garabrandt and James, 2005). In addition to the agency reviews cited in the report (e.g. NTP, IARC, and EPA), several other reviews have also been published on this topic that could be consulted and referenced in the NYDOH report (e.g. see Lavin et al 2000; Mandel and Kelsh 2001; McLaughlin and Blot 1997; Weiss 1996).

Overall, the review of recent studies presents a good summary of research to date since publication of the Wartenberg et al review. As discussed by the committee, it would be nice to see a summary of the studies presented in tables, organized by cancer outcome.

Based on a recently completed review and meta-analysis of occupational TCE exposure and cancer, which was recently presented to the National Research Council Committee on Human Health Risks of Trichloroethylene (Kelsh et al., 2005), and in consideration of opinions expressed in other reviews, I would conclude that the epidemiologic evidence is not as strong as suggested in the NYDOH summary. Instead I would suggest that the epidemiologic evidence is equivocal on some cancer outcomes and not supportive of a causal association for others.

Draft Comments From Recent Meta-Analysis:

Generally the presentation provided with these comments is fairly self-explanatory. I have included additional comments here are for clarification or summarization purposes. The results of this review and analyses are presented as draft comments. Papers summarizing these analyses are either submitted for publication or in preparation.

This analysis focuses on occupational TCE exposure and six cancer outcomes: kidney, liver, NHL, esophageal, leukemia and lung cancers. Only case-control and cohort studies were included in the summary. Community studies, proportionate mortality studies, and studies of laundry workers were not included.

Analysis were conducted separately for:

- All studies that identified a TCE exposed subcohort ("Group I" studies)
- Studies where TCE exposure was noted but individual exposure assignments were not provided or studies had significant design limitations ("Group II" studies)
- Aerospace worker studies (from Group I and Group II)

By exposure intensity (when feasible)
By exposure duration (when feasible)
Studies conducted in the U.S.
Studies conducted in Europe
Case-control studies of kidney cancer and NHL

A key aspect of this review was the assessment of heterogeneity, which addresses the question of how consistent the estimates of risk were across the different studies.

Key findings:

Kidney cancer:

Overall meta relative risk (mRR) was 1.29 (95% CI: 1.06 – 1.57). The mRR for aerospace workers was 1.01 (95% CI: 0.75-1.38). The recent Danish study (Raaschou-Nielson 2003) was the largest cohort study and reported an RR=1.2. However, these results may be confounded by smoking, which was not accounted for and mentioned as a possible confounder by the authors given the excess of lung cancer observed their information about smoking patterns in the cohort. Mixed, inconsistent results were noted across the case-control studies.

Liver Cancer:

Overall mRR for Group I studies was 1.32 (95% CI: 1.05-1.66). Lower summaries for U.S. studies (mRR=0.95, 95% CI: 0.61-1.48) and studies of aerospace workers (mRR =0.86, 95% CI 0.60-1.24) compared to European studies (mRR=1.47, 95% CI 1.13-1.92). Analyses includes both liver and biliary cancers combined (some studies only reported the results for these two cancers combined).

NHL

Mixed finding across different groups of studies. There were higher mRRs were observed for Group I studies (mRR=1.59, 95% CI 1.21-2.08). No significant findings from case control studies, aerospace worker studies, or Group II studies. Among Group I studies, analyses of available data on exposure "intensity" and duration of exposure (although limited in both cases) did not suggest patterns of dose-response.

Esophogeal:

Mixed findings as indicated by low p-values for heterogeneity tests. Analysis limited by small numbers. Hansen and Blair studies report elevated risks, other studies do not report similar elevations. Overall mRR=1.07 (95% CI 0.78-1.46) for total cohort (summary plotted on graph). Overall TCE exposed subcohorts

mRR=1.35 (95% CI: 0.80-2.26) [not shown on graph]. Potential confounders, smoking and alcohol, may bias results.

Leukemia:

No excess risk found in any study groups.

Lung:

No excess risk found in any study groups. Raaschou-Nielson study reported RR=1.2 and suggested that this was possibly due to a higher smoking prevalence in these workers.

Differences in results and interpretations of this meta-analysis compared to Wartenberg et al can be explained by several factors:

- Current meta-analysis includes more recently published studies and summarizes findings for case control studies of kidney and NHL cancers.
- Different grouping of studies (e.g. Henschler study is grouped in Group II studies)
- Differences in which data were abstracted from studies. Our criteria for data abstraction attempted to apply consistent protocols – in some cases resulted in different results abstracted compared to Wartenberg et al.

Limitations of and value of meta-analysis as applied to these studies and limitations of individual studies are discussed in presentation.

Use of Hansen et al study for Quantitative Risk Estimate:

The NYDOH appropriately characterized the Hansen et al study as one of the stronger epidemiologic studies based on the exposure assessment protocols employed in this study. Biomarkers of exposure have the advantage of providing individual quantitative estimates of personal exposure, however they also have the limitations of reflecting only relatively recent exposures (given the half life of TCE and its metabolites). In addition, an average of two measurements are relied upon to reflect an entire work history. The more recent and much larger Danish study by Raaschou-Nielson and colleagues relies on extensive exposure measurement data for classification of the cohort and includes many more workers in the epidemiologic analysis (14,000 + workers compared to 803 in the Hansen et al study). Because of the more statistically precise estimates from the Raaschou-Nielson study, I would recommend using this study as well in validating the air criteria estimates derived from animal studies, using the same approach as applied to Hansen et al data.

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- Reviewer

The question under investigation is the specification of the lowest concentration of TCE in the air that poses unacceptable risk to humans. Theoretically it would be best to use data from human studies to estimate this level. However, the large majority of studies examining human health effects of TCE exposure using only relative exposure values (often based on job titles and job exposure matrices) rather than more comprehensive exposure measurements. The study with the most reliable exposure measurements is that of Hansen et al. (2001), and NYSDOH appropriately used these data to estimate exposure guideline. It also would be worth exploring whether some of the exposure data from the Hansen et al. (2001) study could be used to estimate exposure for the larger Raaschou-Nielsen et al. (2003) study. Another problem with all of the studies, to some degree, is the limited number of people in each study population and the very small number of cases for the outcomes of greatest interest. In addition, there likely is uncontrolled confounding in all of the studies, although I do not believe this undermines the validity of the results.

Using the Hansen et al. (2001) study, NYSDOH estimated TCE air concentrations for three levels of excess risk for esophageal cancer, non-Hodgkin's lymphoma. It would be useful to estimate similar levels based on data for kidney and liver cancer. Kidney cancer is of particular interest given the biological plausibility.

Because the goal is to estimate an air guideline for a specified level of risk to humans, it would be useful to combine the risks from all (or most) of the sites that pose a risk. In that way, the value would address the combined risk of any cancer to a person, rather that having attention focused on only the most sensitive site. (Of course, if one cancer site is far more sensitive, the result of combining risks from several sites will barely be noticeable.)

The recommended air guideline is based primarily on the animal data, with support from human data. The underlying logic is that concordance between animal and human data lend support to the plausibility of causation. However, numerous studies have shown the limited concordance for a single agent among animals of the same species but different genders, same genders but different species, and even lower concordance with human data. Such information should be provided in this report so that readers appreciate that outcomes that occur only in humans may still be relevant and important, and that estimates based only animal data may not adequately represent the underlying human risk.

- Reviewer

Epidemiological study has demonstrated a high relative risk of contracting NHL in relation to exposure to TCE. **Hansen et al. (2001)** conducted a morbidity study of a cohort of Danish workers exposed to TCE. Cohort members were selected for study by the investigators on the basis of information on previous TCE exposure levels, or on the basis of information on a metabolite of TCE, namely trichloroacetic acid (TCA), in the workers' urine. This information was provided to the investigators by the Danish Labor Inspection Services. On the basis of these selection criteria 803 workers (658 men and 145 women) were identified for study. The largest fraction of measurements came from persons working in the iron and metal industry, where TCE was used for degreasing. Job information was reconstructed from the files of the National Pension Fund. Each cohort member was linked to the nationwide Danish Cancer Registry by personal identification number to determine whether they had been diagnosed with cancer. The cohort was followed from 4/1/68 to 12/31/96.

For the entire cohort, the results indicated a statistically significantly elevated Standardized Incidence Ratio (SIR) for NHL; SIR = 3.5 (8 obs v 2.29 exp, $p < 0.05$). The authors also observed a dose response by duration of employment. For those employed for < 6.25 years (75 months) the SIR for NHL was 2.5, (95% CI 0.3 -9.2). For those employed for > 6.25 years (75 months), the SIR for NHL was 4.2 (95% CI = 1.1 - 11.0). Analyses by mean intensity of exposure and by cumulative exposure did not show any dose response for NHL. The authors noted that chance may have played a role in the lack of dose response for the latter two categories of exposure because it was not known whether the measured concentrations of TCE actually reflected true low and high exposure concentrations experienced by the workers. For this reason, the authors were of the opinion that "the more precisely measured duration of employment may represent a more reliable measure of cumulative dose."

Raaschou-Nielsen et al. (2003) evaluated cancer incidence among 40,049 blue-collar workers employed for three or more months in one of 347 Danish companies with documented TCE use. The main industries where the TCE exposures occurred were iron and metal (48%), electronics (11%), painting

(11%), printing (8%), chemical (5%), dry cleaning (5%) and other industries (13%). For NHL in the overall working population, the SIR was 1.2 (95% CI = 1.0-1.5). In a sub-cohort of 14,360 workers presumed to have been highly exposed to TCE, the NHL SIR = 1.5 (95% CI = 1.2-2.0).

For the entire cohort, analyses by latency and duration of employment showed slight increases with increases in these variables. In analyses by year of first employment, the highest risk of NHL was observed for those first employed prior to 1970, when TCE exposures were thought to have been the highest, SIR = 1.4 (95% CI = 1.0-2.0).

The authors stated that some of the workers included in the study probably received little or no TCE exposure, which would bias the results toward the null hypotheses of no association. They also stated that misclassification of duration of exposure could lead to attenuation of an apparent dose-response. They concluded that the association between TCE exposure and NHL found in the study was consistent with the results of the most reliable cohort studies, and that the findings could be considered as independent from a similar finding in their previous study **(Hansen et al. 2001)** because overlap between cases of NHL was negligible; only two NHL cases were included in both studies.

Axelson et al. (1994) conducted a cohort mortality and morbidity study of 1670 workers exposed to TCE in Sweden between 1955 and 1975 and followed them through 1985. Cohort members were identified from their participation in a survey to determine trichloroacetic acid (TCA) levels in their urine. The overall cancer morbidity among men was slightly lower than expected, SIR = 0.96, while for NHL the SIR = 1.56 (95% CI = 0.51-3.64). This result is not statistically significant, however, it is 50% higher than the death rate for all causes of death and as a result provides some information in conjunction with other study results related to TCE and lymphoma. The authors concluded that there was no evidence that TCE was a human carcinogen when the exposure is as low as it was for the workers studied, e.g., < 20 ppm for 81% of the cohort members. In my opinion, this report provides some limited evidence of an elevated risk of NHL in relation to TCE exposure, or exposure to chlorinated solvents.

Hardell et al. (1994) conducted a case-control study of 105 cases of NHL admitted to the Department of Oncology in Umea, Sweden between 1974 and 1978. Exposures to toxic chemicals for these cases were compared to that of 355 controls matched for age, sex, place of residence and vital status. Analyses demonstrated a significantly elevated odds ratio (OR) for NHL and exposure to organic solvents. More specifically, for TCE the OR = 7.2 (95% CI = 1.3-42). The authors concluded that their study demonstrated an increased risk of NHL in relation to organic solvents exposure. **[Note: This report is not cited in the NYDOH report and should be added.]**

Anttila et al. (1995) studied cancer incidence from 1967-1992 among a group of Finnish workers exposed to TCE, tetrachloroethylene (PCE) and 1,1,1-trichloroethane (TC). The vast majority of these workers were exposed to TCE. Regarding NHL for the entire cohort, the SIR = **2.13 (95% CI = 1.06-3.80)**. When the data were categorized by years since first measurement of exposure (latency), for those with 0-9 years the SIR = 1.21 (95% CI = 0.15-4.38); for those with 10+ years of latency, the SIR = 2.55 (95% CI = 1.17-4.84) based on 9 cases. These results indicate an overall significant excess of NHL among these workers and also an increase in NHL with an increase in latency. When the data were analyzed for the three solvents separately, the SIR (TCE) = 1.81 (95% CI = 0.78-3.56). While this result is not statistically significant overall, the data for those exposed to TCE demonstrate an increase in the relative risk of NHL with an increase in latency. Since one would expect that the risk of NHL would increase with an increase in the latency period, these data provide further evidence of an association between TCE and NHL in this study. The SIRs by latency category are as follows: 0-9 years = 0.83; 10-19 years = 1.75; 20+ years = 3.24.

For workers in the **Anttila et al. (1995)** study who were categorized by PCE and TA exposure separately, the SIRs were 3.76 (based on 3 cases) and 3.87 (based on 1 case), respectively. The authors concluded that their study provided evidence to support the hypothesis that "trichloroethylene and other halogenated hydrocarbons are carcinogenic for the liver and lymphohematopoietic tissues, especially non-Hodgkin lymphoma."

Blair et al. (1998) followed to the end of 1990 a cohort of 14,457 men and women aircraft maintenance workers exposed to TCE and other organic solvents and chemicals in order to evaluate their cancer risks. For workers categorized as exposed to TCE, the overall SMR for NHL for men was 2.0 (95% CI = 0.9-4.6) and that for women was 2.2 (95% CI = 0.4-10.0). The SMRs for NHL increased slightly with period of followup. For those followed to the end of 1982, the SMR for NHL was 1.9 and for those followed from 1983 through 1990, the SMR for NHL was 2.2. None of these results were statistically significant. However, the observation of such large relative risks of death from NHL being non-statistically significant is likely a reflection of low statistical power.

Blair et al. (1998) also performed analyses by units of exposure to TCE. In these analyses they did not observe a dose response in terms of an increase in exposure to TCE being accompanied with an increase in the risk of death from NHL. The SMRs by three increasing units of TCE exposure were 1.8, 1.9 and 1.1, respectively. The latter SMR, however, was based on only five deaths from NHL and as such provides little statistical power to evaluate relative risk for this categorization of exposure. Moreover, the 95% CIs for the latter data point indicate that the risk of death from NHL could have been as high as 3.8. In doing their dose response analysis for TCE, the authors did not control for exposure to other organic solvents which are known to be associated with an elevated risk of NHL. Their own study also suggests an elevated risk for NHL in relation to "other

organic solvents." For example, workers in the **Blair et al. (1998)** study categorized as "not exposed to TCE" demonstrate an overall SMR for NHL for men of 1.6 (95% CI = 0.5-4.5) based on 11 deaths. For women "not exposed to TCE" the SMR for NHL was 2.0 (95% CI = 0.3-12.2) based on two deaths. Thus, **Blair et al. (1998)** have exposure confounding from other potential causes of NHL in their dose response analysis for TCE and NHL. This factor, along with the lack of statistical power may have been responsible for the investigators not being able to observe a dose response in their study for exposure to TCE and risk of death from NHL.

Although the **Blair et al. (1998)** findings do not demonstrate a statistically significant excess of NHL among the workers exposed to TCE and other organic solvents, they do provide some evidence that exposure to TCE and other organic solvents are associated with an elevated risk of death from NHL. **Blair et al. (1998)** commented that the observed non-significant excess of NHL in relation to TCE occurred in both follow-up periods, but that the associations do not seem to be specific to TCE because workers exposed to other chemicals also experienced increased risks for NHL.

Boice et al. (1999) conducted a cohort mortality of 77,965 workers employed for at least one year on or after 1960 at California aircraft manufacturing facilities operated by Lockheed Martin. Of these, 45,325 were "factory" workers and of these 2,267 (5.0%) were considered exposed to TCE. Vital status was determined through 1996. In comparison to the State of California general population rates of death for whites and to the U.S. general population rates for non-whites in the study, overall, there was a significant deficit of mortality from all causes among "factory workers," SMR = 0.87. For NHL, the SMR for the entire "factory worker" population, most of whom were not exposed to TCE, was 0.94. Analyses of data for "factory workers" for death from all causes by duration of employment demonstrated a significant deficit of mortality for all duration of employment categories. For those employed < 10 years, 10-19 years, 20-29 years and > 30 years the SMR for all causes was 0.94, 0.90, 0.85, and 0.78, respectively. This trend shows an inverse relationship for risk of death from all causes by duration of employment. Furthermore, all of the major diseases from which people die (heart disease, all malignant neoplasms, lung cancer, non-malignant respiratory disease) demonstrate an inverse relation with duration of employment. The logical extension of this observation is that if one worked long enough at Lockeed Martin, they would never die. These observations suggest that the authors have a major methodological problem in their study. I suggest that they may have mis-allocated person-years of follow-up, or there may be some selection bias in the study. [See **Wagoner et al. 1976** for evidence of an inverse relation for risk of death by duration of employment being attributable to mis-allocation of person-years of followup.] To the contrary, the SMRs for NHL indicate a positive trend for increase in the risk with each succeeding increase in duration of employment category. The SMRs for NHL by

duration of exposure categories mentioned above were 0.75, 0.80, 0.92 and 1.32, respectively.

Based on internal comparisons, the risk of NHL also increased in a monotonic fashion with years of exposure. For those exposed < 1 year, 1-4 years and > 5 years, the SMRs for NHL among those categorized as exposed to TCE were 0.74, 1.33 and 1.62 respectively. The trend value was $p > 0.20$. Based on these analyses and contrary to the author's opinion, these findings suggest an association between employment in manufacturing at these facilities and an elevated risk of NHL. More specifically, they also suggest an association between exposure to TCE and NHL, and that these associations are underestimated.

Morgan et al. (1998) conducted a cohort mortality study of 20,508 aerospace workers from the Hughes Aircraft Company. Of these 4,733 were reported as having had occupational exposure to TCE. Workers were included in the study if they had at least six month of employment at the facility between 1950 through 1985. Vital status was determined through 1993. Industrial hygiene measurements were limited prior to 1975. Therefore, employees with at least 30 years of experience rated TCE exposures for each job classification. In addition to atmospheric exposures, employees were exposed to TCE through drinking water and wash water. These latter exposures, however, were not considered in classifying occupational exposures to TCE even though they are known to be "an important route of human exposure" **(Bogen et al. 1992).**

For workers exposed to TCE, the SMR for NHL was 0.96, (3 obs. v 3.1 expected). When workers were categorized by TCE exposure as "low" or "high," those with low exposure had an SMR for NHL of 1.79 (2 obs v 1.12 exp). For those categorized with high TCE exposure the SMR was 0.50 (1 obs v 2.00 exp).

The authors concluded that their study found no support for any cancer risk among workers exposed to TCE. They qualified their findings, however, by stating that the number of cases of cancer in the TCE sub-cohort limited their ability to assess the risks for rare cancers. [Note: NHL is a rare cancer.] They also stated that they lacked data on confounders and had no direct measurement of exposure to TCE, nor to other chemicals found in the workplace, and that exposure groups were narrow which would result in imprecise estimates of relative risk. I agree with the authors qualifications about their study conclusions.

In my opinion, the **Morgan et al. (1998)** study provides little if any meaningful data upon which to evaluate the risk of NHL among workers exposed to TCE. The authors essentially had no data on exposure and relied on relative exposures as determined from 30-year employees, who had to estimate exposures going back more than 40 years. Second, there were only three deaths from NHL among those exposed to TCE (versus 3.1 expected), which they placed in two dose-response exposure categories. Evaluating dose

for TCE exposure and NHL were consistent across the three most informative studies indicating a modest excess relative risk, with 27 observed and 18.9 expected cases. They also stated that the risk was not increased in the two less informative studies. In a case-control study of malignant lymphomas, they noted that an elevated odds ratio was observed for exposure to TCE on the basis of seven exposed cases. They concluded there was some evidence for increased risks of cancer of the liver, biliary tract and for NHL following exposure to TCE.

At the request of the Halogenated Solvents Industry Alliance (HSIA), **Weiss (1997)** published a limited review (data from only five studies were evaluated) of four cohort studies of workers exposed to TCE, and of one case-control study of individuals with NHL. The author stated that the data suggested that NHL seemed to develop more commonly among workers exposed to TCE than in members of the general population. However, overall, he was of the opinion that the epidemiological data for TCE and cancer that he reviewed were limited.

In it's *9th Report on Carcinogens* (2000), the **National Toxicology Program (2000)** concluded that TCE was "reasonably anticipated to be a human carcinogen" based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of malignant tumor formation in experimental animals, and convincing relevant information that trichloroethylene acts through mechanisms indicating it would likely cause cancer in humans." One of the sites of concordance mentioned for the observation of cancer in animals and humans was lymphomas.

Wartenberg et al. (2000) conducted a review of the available epidemiological literature related to TCE and cancer. Included in their review were occupational cohort morbidity and mortality studies, case-control studies and community-based studies. Occupational cohort studies were categorized into three tiers. The first tier comprised studies wherein urinary biomarkers of TCE exposure (trichloroacetic acid, or TCA) were available. The second tier included studies where qualitative information on exposure derived from occupational histories were available. The third tier of studies comprised individuals employed as dry cleaning or laundry workers.

The authors concluded that tier one studies provided evidence of a positive association between TCE exposure and NHL. **They also noted that TCE exposures to workers in these studies were relatively low, with 80% of the cases being exposed to an average of less than 20 ppm.** The results from tier two and three studies were considered null in that there was only weak evidence for an association between TCE and NHL. The authors concluded that the case-control studies provided evidence of an association between solvents, and specifically TCE and NHL. They also concluded that the findings from two community based studies, where the route

of exposure to TCE was through town water contamination, supported an association between TCE and NHL.

Wartenberg and Scott (2002) updated the cohort morbidity study results from their earlier review **(Wartenberg et al. 2000)** by adding data from the **Hansen et al. (2001)** study. Their new calculations for NHL in relation to TCE exposure indicated a total of 30 cases of NHL, SIR = 1.9 (95% CI 1.3-2.8). The authors concluded that the new data provided additional support for their previous conclusions that TCE exposure causes cancer in humans. The authors further noted that only a small number of subjects in the **Hansen et al. (2001)** study experienced exposures higher than the current permissible limit suggesting that the cancer risks from exposure to TCE may be associated with low-level exposure.

The Environmental Protection Agency has developed a "draft" Trichloroethylene Health Risk Assessment **(EPA 2002)**. Regarding TCE and lymphoid tumors, EPA stated that "among the epidemiological studies, the data appear strongest overall for liver cancer and also, to some degree, for lymphoma....Tier 1 studies show excesses for Hodgkin's Disease, non-Hodgkin's lymphoma, and multiple myeloma. The addition of a recently published study by Hansen et al., significantly adds to the weight-of-evidence for lymphoid tumors."

More recently, **Huff et al. (2004)** published a commentary on TCE and cancers in humans. Based upon their review of experimental cancer data and epidemiological study results, they concluded that "TCE is indeed clearly coupled with ....non-Hodgkin's lymphoma.... In our view, these collective findings of TCE worker exposures and resultant cancers should now be considered unequivocally as sufficient and persuasive evidence to classify TCE as a human carcinogen." Note worthy among the co-authors of this review is Dr. Lorenzo Tomatis, former Director of the World Health Organization's International Agency for Research on Cancer (IARC), the WHO expert agency for determining the causes of cancer in humans.

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B. REVIEWS OF EVIDENCE FOR THE ASSOCIATION BETWEEN EXPOSURE TO ORGANIC SOLVENTS AND NON-HODGKIN'S LYMPHOMA

A number of review articles also have concluded that organic solvent exposure is related to an elevated risk of NHL. **Brandt (1987)** presented the findings of several studies and concluded that organic solvents were associated with an increased risk of NHL. He also called attention to the elevated risk of NHL identified in his study that was not yet published, NHL OR = 3.3 (95% CI = 1.9-5.8), e.g., **Olsen and Brandt (1988)**. **Pearce and Bethwaite (1992)** concluded that studies have found an increased risk of NHL in work involving exposure to solvents or related chemicals. **Weisenburger (1994)** was of the opinion that studies suggesting an etiologic link between solvent exposure and other chemical exposures and NHL have recently been confirmed. **Persson (1996)** concluded that solvent exposure and malignant lymphoma have been observed in a great number of studies and that occupational exposure to solvents plays a role in the epidemiology of NHL.

Rego (1998) evaluated the literature for associations between NHL and exposure to organic solvents. He concluded that in 25 of the 45 studies he reviewed (55.5%) from 1979-97, there were 54 statistically significant associations between NHL and solvent exposures. Among studies in which solvent exposure was more accurately defined, 13/18 (72.2%)suggested organic solvents as a risk factor for NHL, OR = 5.2 (95% CI = 1.11-26.19).

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6. Is the summary transparent and does it adequately justify the guideline of 5 mcg/m^3?

- Reviewer

This is a loaded question. A few comments/questions for now.

Does this document need to be completed before the NAS TCE report?

I have not seen a consensus group agree on the statement on page 167, line 28; that there 'is a positive association between TCE exposure and several types of cancer for humans'. This statement is made in a few other places. I can not comment on this, only to say this statement would be viewed as controversial, at best, by several people.

For noncancer, I will try to send a good review paper of TCE and cardiac malformations that will be published within a week or so (on-line version). This may influence the views of NYS on this subject.

The summary tables/text should include details about the routes of administration of TCE for deriving each air criterion. Can you tabulate the potency estimates for inhaled TCE vs other routes of administration for animals and human, then compare to each other? Both cancer and non cancer effects can be evaluated in this manner. I think this will strengthen the document when it summarized in this fashion. I think inhaled TCE should be given the highest priority for cancer, at least. I commend the authors/analysts of this document in using the inhalation studies in mice (Maltoni, 1986) for cancer potency estimates and not the NCI and NTP oral bolus dosing studies.

The number 5 ug/m3 or 0.9 ppm is not particularly transparent. Maybe a figure or visual representation of the criterion values may help in showing how the value was selected. I was not sure how this particular number was derived.

I think of epigenetic mechanisms when I think of TCA as the primary metabolite responsible for liver cancer in mice. The low dose extrapolation approach suggests that a genotoxic mechanism is operative. This aspect of the work warrants discussion in the text.

- Reviewer

The summary is well-written, concise and it does an excellent job in highlighting the major studies and issues that impact the derivation of an air guideline for TCE. However, the selection of 5 mcg/m3 as the guideline is not fully justified. Based on the available data, especially the cancer data, a guideline in the range

of 1-5 mcg/m3 could be justified. After all, a linear model cannot be rejected, for some sites acceptable risk levels are less than 5 mcg/m3 and in some cases less than 1 mcg/m3 and EPA has stated that TCE is highly likely to be a human carcinogen. The NYDOH may wish to consider an acceptable risk level to be 3-5 cancers per million since TCE appears to be on the cusp between a known human carcinogen and a probable human carcinogen.

- Reviewer

While the document overall is clear and well written, the development and justification for the guideline of 5 mcg/m3 could be made more transparent. For example, it would be helpful to know what process was used to choose the value of 5 from the many numbers produced in the report. It would be helpful to know how results for children were used in conjunction with that for adults. (In fact, that issue is not addressed consistently through the report but should be, with assessments for risks to children provided with most assessments for risks to adults are appropriate.) It is important that this final step be made more transparent, including an explanation of why the guidelines below 5 mcg/m3 were not recommended.

- Reviewer

Children represent a population which is particularly susceptible to the adverse effects of environmental toxins. They breathe more air, drink more water and eat more food per pound of body weight than adults. They also occupy different breathing zones and spend a disproportionate amount of time in certain locations than adults. Therefore, their effective dose is much higher than adults living amongst the same exposures. Additionally, the developing brain is particularly susceptible to the effects of neurotoxicants, such as TCE. Child-based PBPK models for methylene chloride and tetrachloroethylene were developed to determine if age-specific groups are more sensitive to chemical exposures than adults. Thus far, results of the modeling efforts show that neonates are 3 to 10-fold more susceptible to chemical toxicity via inhalation and oral routes than adults exposed to identical environmental conditions (*ATSDR: Computational Toxicology Laboratory*).

TCE is a chemical solvent which is heavier than air. The concentrations in a room will be highest at the level where children spend most of their time, close to the floor. The gradient may be high enough to cause a marked difference in exposures. Current proposed collection protocols for samples in indoor air from vapor intrusion call for sampling to take place at a height of 3 feet off the ground (NYS DOH: 2005). The most vulnerable group of children are under the age of two. This means than more than 75% of all boys and 95% of all girls will be subject to higher levels than those measured when they are standing in those rooms. Since children also spend time sitting and playing on the floor this applies to 100% of all children occupying these spaces.

Children breathe more air per pound of body weight than adults and their metabolic rates are higher relative to their size. Thus they consume more oxygen than adults and produce more carbon dioxide per pound of body weight. This increased CO2 production requires higher minute ventilation. Minute ventilation for a newborn and adult are approximately 400 mL/min per kilogram and 150 mL/min per kilogram, respectively. Thus children's exposure may be greater than that of adults. The discussion should justify clearly how the air criteria takes this 3 to 4 fold difference into account, especially in regards to the mathematical modeling of theoretical internal concentrations of active metabolites.

Neurodevelopmental disorders (NDDs) including learning disabilities, dyslexia, mental retardation, attention deficit disorder, cerebral palsy and autism affect 5-10% of babies born worldwide. Subclinical decrements in brain function are also widespread and affect tens of millions of children. Some observers report that prevalence of certain NDDs – ADHD and autism, in particular - may be increasing, but data to sustain that position are limited. NDDs disrupt the lives of patients and families. They place great burdens upon society. Their treatment is difficult, and the disabilities they cause can often last lifelong.

The developing human brain is inherently much more susceptible to injury caused by toxic agents than the mature brain of an adult. This susceptibility reflects the fact that in the nine months of prenatal life the human brain must evolve from a strip of cells along the dorsal ectoderm into a complex organ comprised of billions of precisely located, highly interconnected cells. Neurons must move along specified pathways from their points of origin to their assigned locations, they must establish connections with other cells near and distant, and they must learn to intercommunicate. For optimal CNS development, all of these processes must take place within a tightly controlled time frame, in which each developmental stage must be reached on schedule and in the correct sequence. Because of the extraordinary complexity of human brain development, there are windows of unique susceptibility to toxic interference that have no counterpart in the mature brain, or in any other organ. If a developmental process in the brain is halted or inhibited, there is little potential for later repair, and the consequences are often permanent. Postnatally, the human brain continues to develop, and the period of heightened vulnerability therefore extends over many months through infancy and into early childhood. While most neurons have been formed by the time of birth, growth of glial cells and myelinisation of axons continue for several years. A broader discussion in the summary of the review of literature regarding the affect of TCE on neurodevelopment and behaviour should be included.

TCE and at least one its breakdown products, DCA, are recognized neurotoxicants. In the introduction of the article by White, RF et al., 1997, the authors summarize the potential mechanisms for the neurotoxicity of TCE. It may be mediated by peroxidation of cell membrane lipids or by specific effects on regulation of membrane fatty acid composition. The narcotic effect of TCE, an

outcome used to define its neurotoxicity, may result from disturbed physical-chemical properties of nerve membrane or from an increase in the activity in one or more of the phospoinositide-linked neurotransmitter systems. Animal studies clearly indicate that administration of TCE produces a loss of myelin sheaths in the temporal and occipital cortex as well as in the spinal cord and modifies lipid content in the trigeminal nerve. Furthermore, TCE damages oligodendrocytes in the hippocampus. In this study of neurobehavioral effects, the authors investigated three groups of residents who were exposed to TCE in well water. A high rate of cognitive deficits of the type seen in patients with CNS dysfunction attributable to solvent exposure was seen. Individuals who were exposed during childhood (before age 18) showed a greater range of deficits than individuals who were exposed as adults. These findings suggest that chronic environmental exposure to solvents produces more diffuse CNS damage in children and that children with such exposures are especially likely to develop learning disabilities (White RF et al., 1997).

Reif et al. studied a population-based sample of 143 residents of a community in Denver in which the municipal water supply had been contaminated with trichloroethylene (TCE) and related chemicals from several adjacent hazardous waste sites between 1981 and 1986. This study adds to the evidence that long-term exposure to low concentrations of TCE is associated with neurobehavioral deficits (Reif JS et al., 2003). This was a study exclusively of adults, a much less sensitive population than children. These two studies are based on orally ingested TCE. In light of the paucity of research investigating the relationship between neurodevelopment, or neurophsychological testing in general, and the important of this crucial issue we recommend that they should be considered for inclusion in the review.

TCE is commonly found in combination with its breakdown products or other toxic compounds used by the same industry. For instance, ATSDR prepared an interaction profile for 1,1,1-Trichloroethane, 1,1-dichloroethane, Trichloroethylene and tetrachloroethylene. This mixture was found in groundwater sample from 95% of NPL sites, in soil samples from 23% of the sites and in air samples from 12% of the sites. Their conclusion was to use a model that assumes additive joint toxic action based on neurological impairment (ATSDR, 2004). An additional justification for additional protective factors, especially when translating the findings of animals studies, is the potential for an additive effect on neurological outcomes.

At least one time in this report, an average weight of 20.5 kg was used to represent the average weight of children. Page 41 line 3: Assuming the average weight of a child is 20.5 kg but the average weight of children varies by age. Probably, the most important time to protect children from the neurotoxic effects of TCE is during brain development. According to the CDC, the 50th percentile weight for newborn girls and boys is 3.4 kg and 3.6 kg respectively. By the age of 2, when most central nervous system development is complete, the 50th percentiles are 12 kg and 12.8 kg respectively. Applied to your initial calculation,

the child adjusted LOEL for CNS effects would be 4.3 mg TCE/m3 to 16 mg TCE/m3 at the limits of these parameters. The derived air criteria based on this study after applying an interspecies uncertainty factor of 10, a child protective factor of 10 due to increased susceptibility and an uncertainty factor of 10 to account for the use of data obtained in a study with less-than-chronic exposure would be 4.3 µg/m3.

Pediatrics is built on the understanding that children are not just little adults. Taking this into consideration allows a better understanding of how to prevent harm from toxins in their environment. In consideration of an air criteria based on studies showing the adverse effects of TCE on adults and animals, a level of 5 µg/m3 may be suitable for adults, excluding pregnant women and possibly women of childbearing age. However, this same level may not adequately protect more vulnerable populations such as the fetus, the newborn and children of all ages. Therefore we ask that in light of the paucity of scientific studies that look at neurodevelopmental outcomes in this population, a more precautionary air criteria be considered in spaces that may be occupied by children. This includes schools, daycares, housing developments and recreational facilities. One possibility for determining an acceptable air level of TCE is to consider a level which is closer to background levels found in homes across New York State.

The Food Quality Protection Act, the principal federal statute on pesticides, which is based on the 1993 NAS report on *Pesticides in the Diets of Infants and Children*, requires EPA to impose a 10-fold child-protective safety factor into pesticide standards, when

(a) there exist data showing that children have greater or different susceptibilities than adults, *or*

(b) no specific examination of pediatric and developmental toxicity of a particular chemical has been undertaken.

It would appear that the second of these two situations pertains to TCE, since there appear to be no epidemiological or developmental toxicological studies of TCE that have specifically assessed its potential to cause functional impairment in the developing brain.

Recommendations:

- The summary needs to be clearer on how this air criteria takes the unique vulnerabilities of children into account. For instance, where in the models are they represented and how the protective factor was applied.
- The discussion should justify clearly how the air criteria takes the 3 to 4 fold difference in minute ventilation between adults and children into account, especially in regards to the mathematical modeling of theoretical internal concentrations of active metabolites.

- A broader discussion in the summary of the review of literature regarding the effect of TCE on neurodevelopment and behaviour should be included.
- Two studies, White et al. and Reif et al., although they are based on orally ingested TCE, should be considered for inclusion in the review.
- A further justification for additional protective factors, especially when translating the findings of animal studies in which a single exposure was measured, is the potential for an additive effect of multiple contaminants on neurological outcomes.
- Further consideration should be given to the dynamics of early childhood growth and development. This includes developmentally appropriate behaviors such as playing on the floor.
- Consideration of a two tiered air criteria which takes a precautionary approach should make the air criteria in spaces that are occupied, or potentially occupied, by children closer to background air levels.

Additional Studies:

White RF, Feldman RG, Eviator II, Jabre JF, Niles CA. Hazardous waste and neurobehavioral effects: a developmental perspective. Environ Res. 1997;73(1-2):113-24.

Reif JS, Burch JB, Nuckols JR, Metzger L, Ellington D, Anger WK. Neurobehavioral effects of exposure to trichloroethylene through a municipal water supply. Environ Res. 2003 Nov;93(3):248-58.

Other References:

ATSDR. 2003. Computational Toxicology Laboratory. http://www.atsdr.cdc.gov/ribfactsheets/comtox.html last updated June 14, 2004. Accessed on August 23, 2005.

ATSDR. May 2004. Interaction Profile for: 1,1,1-Trichloroethane, 1,1-Dichloroethane, Trichloroethylene, and Tetrachloroethylene. U.S. Department of Health and Human Services. Public Health Service.

Landrigan, PJ, Kimmel, C, Correa A, Eskenazi B. Children's health and the environment: public health issues and challenges for risk assessment. Environ Health Perspect. 2004 Feb;112(2):257-65. Review.

NYS DOH. February 2005. Guidance for Evaluating Soil Vapor Intrusion in the State of New York. Public Comment Draft. Bureau of Environmental Exposure Investigation.

To convert concentrations in air (at 25°C) from ppm to mg/m^3: mg/m^3 = (ppm) x (molecular weight of the compound)/(24.45). For trichloroethylene: 1 ppm = 5.37 mg/m^3. To convert concentrations in air from µg/m^3 to mg/m^3: mg/m^3 = (µg/m^3) x (1 mg/1,000 µg).

- Reviewer

I assume this means the Executive Summary. The summary is certainly transparent, and provides a high-level abstract of the draft report.

Given the summary only, one would think that the guideline of 5 µg/m^3 is justified. However, the relevant question is not whether the Executive Summary justifies the proposed guideline, but rather, does the science that the Executive Summary summarizes justify the proposed guideline? That question is moot.

The proposed guideline of 5 µg/m^3 is based on the Summary Table 8.1. It is not clear by what procedure the guideline was obtained. After a lengthy, comprehensive, and authoritative review of the scientific literature, just two paragraphs at the end of the draft study are devoted to the derivation of the actual number (p. 174, "a TCE air guideline of 5 mcg/m^3 was selected"). Presumably, the number was based on some sort of weighted averaging procedure, or on an estimate based on the professional judgment of the DOH, or some other criteria. The causal reader might think that the number was pulled out of a hat. The explicit procedure used to obtain the number 5 µg/m^3 needs to be stated.

The appropriateness of the scientific reasoning to derive the number 5 µg/m^3 from Table 8.1 is not clear. The DOH has done an excellent job in reviewing critically the scientific literature and arriving at a well-justified air criterion for the effect of TCE on various animal and human systems separately. The selection of 5 µg/m^3 from this data implies that there was some sort of homogenization or averaging of the numbers: the numbers range from 1 (liver) to 40 (CNS), and the number 5 was taken as the air criterion. The averaging over different target/organ systems does not seem to be justified scientifically. The DOH should consider treating the effect of TCE on each target/organ system separately, and chose the most protective level based on each system, rather than averaging the numbers. If this procedure is followed, an air criterion of 1 µg/m^3 is obtained (from liver cancer).

The guideline in this draft document, like other proposed and adopted guidelines for TCE concentrations in air, is driven by cancer considerations. The 2001 EPA draft study, endorsed by its scientific review board, proposed a range of cancer slope factors which lead to a low end air criterion of 0.02 µg/m^3. The EPA draft study was used to set sub µg/m^3 guidelines in some EPA Regions but not in others. In New York State, the triggers for mitigation of TCE in homes differ by an order of magnitude in various parts of the state, leading to confusion about just what is a safe air level. The NYS DOH draft document (Appendix A) states

that the EPA was in error by including three studies that did not meet the criteria for dose-response assessment. The arguments made in Appendix A are justified. However, given the confusion and variation in operational guidelines set by various federal and state agencies, this draft document needs to be more explicit and transparent in just why its guideline is much higher than guidelines derived from the 2001 EPA draft study.

The extensive review of the cancer literature in the draft document seems to indicate TCE levels giving 1×10^{-6} increased cancer risk can be in the range 0.1-1 $\mu g/m^3$ (e.g., p. 132, 133, 141, 147, 149, and 150 of the draft document), which prima facia would support an air criterion of below 1 μ/m^3. The DOH weighted these studies less. However, given the support on this scientific review panel for weighting the non-Hodgkin's lymphoma more strongly, an air criterion of less than 1 $\mu g/m^3$ might be justified.

Other comments:

Background air concentrations of TCE in the United States are on the order of 0.03 (rural) and 0.46 (urban) ppbv (ASTDR, 1997), which translate into 0.2 (rural) and 2.4 (urban) $\mu g/m^3$. Other surveys (table 7-1 of the draft document) also indicate some elevated levels of background TCE concentration in air. These concentrations are similar to the guidelines proposed by EPA, NYS DOH, and other state agencies. There should be more detailed discussion in the draft document about how ambient air concentrations at or above proposed guidelines will affect toxicity.

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Summary Points from TCE Review Panel Discussion of Health Statistics Review

1. **Does this health statistics review affect the discussion/conclusions about trichloroethene's toxicity in the criteria document in a substantive manner?**

- Members of the panel stated that the ecological design of the health statistics review prevented it from being utilized as part of the toxicological review and risk assessment in the air criteria document. However, the panel expressed appreciation for receiving the review for consideration and noted that the health statistics review provided relevant ancillary information.

2. **Do you have any comments or suggestions about follow-up activities, including those we are recommending?**

A variety of comments were made about appropriate follow-up due to the review's findings of elevations.

- Some reviewers expressed the opinion that the results did merit some type of follow-up, particularly to examine residential, occupational and smoking histories as well as to additionally evaluate whether socioeconomic factors played a role in the findings.

- Further analyzing information from existing sources, such as particular cell type listed in the Cancer Registry, was suggested.

- Some reviewers suggested that birth outcomes merited more attention for follow-up since the latency period is shorter than for cancer, making environmental exposure assessment more feasible.

- Some reviewers suggested that better quantification of exposure, including a variety of exposure routes and sources, would strengthen follow-up steps.

- Some reviewers cautioned that the small numbers of health outcomes would make it difficult to conduct a case-control study for the Endicott study area alone. The suggestion was made to consider studying multiple sites across New York State with similar exposures to increase study power. Questions were raised, however, about the utility of additional study using case-control methods and a larger total population due to the lack of power for studies of such rare health outcomes, such as heart defects. Concerns were also expressed about finding areas with similar exposures.

- Another issue pointed out as a limitation of conducting additional study was that a second study might provide false negative or false positive findings due to factors not able to be controlled such as population mobility, small numbers, or exposure misclassification.

- Some reviewers mentioned that recall bias would be an issue for a case-control approach. Others noted that recall bias was less of a problem for basic information such as smoking, employment and residential histories.

- One reviewer noted that the suggestive excess in lung cancer suggests that smoking might be a factor in the kidney cancer excess, and some type of limited follow-up that could address this issue was warranted.

- One reviewer stated that follow-up studies that might be appropriate can have two different goals: advancing scientific knowledge about the relationship of TCE exposure and health outcomes or as part of a response plan to address community concerns. Any follow-up study undertaken should be able to accomplish one of these two goals. The distinction between these two goals should be considered in developing a follow-up approach and should be discussed with the community.

- Reviewers emphasized continued communication with the community, including explanations of the strengths, limitations, and abilities of proposed steps.