

# **Report of the Peer Consultation Meeting on Toluene**

**Submission by  
American Chemistry Council Benzene, Toluene, and  
Xylenes Consortium  
for the  
Voluntary Children's Chemical Evaluation Program  
(VCCEP)**

**November 7 and 8, 2006  
Erlanger, Kentucky**

**Peer Consultation Organized by  
Toxicology Excellence for Risk Assessment  
(<http://www.tera.org/peer/vccep>)**

**January 16, 2007**

## NOTE

This report was prepared by scientists of *TERA* and reviewed by the panel members. The members of the panel served as individuals on this panel, representing their own personal scientific opinions. They did not represent their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent the opinions of their employers or those with whom they are affiliated.

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*Appendix D – Sponsors’ Errata Page and Expanded Household Products Database*

## Executive Summary

A panel of scientists with expertise in toxicology, epidemiology, exposure, risk assessment, and children's health met on November 7 and 8, 2006, to conduct a peer consultation of a submission on toluene (CAS No. 108-88-3). The American Chemistry Council Benzene, Toluene, and Xylenes VCCEP Consortium and their contractors prepared the submission for the Voluntary Children's Chemical Evaluation Program (VCCEP). The purpose of the meeting was to provide a science-based forum to discuss whether the existing data are adequate to characterize the risks of toluene to children, and if not, to identify data needs. The sponsors and authors of the toluene submission provided the panel with presentations on the submission's assessments of hazard, exposure, risk characterization, and data needs. The panel then discussed the individual assessments, the available data, and data needs.

For the hazard assessment, one presenter summarized the animal toxicity data and a second presenter summarized the human case studies and epidemiology data. The first presenter said sufficient toxicity data on toluene are available to address all of the VCCEP hazard endpoints, and she summarized the Tier 1, 2, and 3 *in vitro* and animal studies that had been conducted. She concluded that the most sensitive endpoint for toluene hazard assessment was neurotoxicity. Toluene also showed developmental toxicity, and some studies showed inconsistent findings of immunotoxicity. Reproductive performance and fertility were not affected. Toluene was non-genotoxic and non-carcinogenic.

In summarizing the human data, the second presenter discussed the association between maternal toluene exposure and infertility. He also noted individual case reports, which suggested that women exposed to high levels of toluene during pregnancy might experience symptoms similar to fetal alcohol syndrome. Neurological effects were described from human behavioral and sensory studies, with the most sensitive endpoint being decreased color discrimination. The presenter said there is some evidence associating toluene occupational exposures with spontaneous abortions but that such findings should be treated cautiously because of several factors that may have artificially elevated the risk ratio. Toluene is classified as "not identifiable as a human carcinogen" by the International Agency for Research on Cancer (IARC).

The panel discussed a number of issues with regard to the hazard assessment. Panelists discussed the differences between adult and neonate responses to toluene observed in the animal studies. Most panel members thought the primary cause of these differences was incompletely developed metabolic capability in the young animals, but some said age-related differences in tissue susceptibility might also play a role. Some panelists emphasized the importance of the neurotoxicity findings seen in both animals and humans. They discussed the difficulty in extrapolating specific neurotoxic effects across species because of the different times of brain development relative to birth. They also discussed the windows of vulnerability that exist during development and how these windows might vary among laboratory animals and humans. Panel members pointed out that, despite many available studies, the overall human database contained substantial weaknesses. Members of the panel also expressed concerns on other hazard-related issues. Several panelists stated the hazard database was weak on the subpopulations of nursing infants through adolescents. One panelist thought that if physiologically based pharmacokinetic (PBPK) models were applied to the available hazard studies, it should be possible to generate data on toluene's blood and tissue levels at essentially all time periods needed to address the subpopulations of interest. Another panelist cautioned that neurotoxic effects of toluene that were termed "subclinical" in humans should not be dismissed as unimportant because these effects might have irreversible consequences if exposure occurred during a window of vulnerability.

The sponsor's presentation on exposure described the procedures and assumptions used for data collection and for modeling. Exposures were placed into three groups: background chronic ambient

exposures, source-specific chronic exposures, and source-specific short term episodic/occupational exposures. Inhalation, ingestion and dermal exposure routes were considered. Typical and high-end values were identified for seven age groupings. Six representative scenarios were presented: residential metal parts degreasing, residential spray painting, residential spray shoe polish, residential mixed media art, tobacco smoke, and occupationally exposed mothers. Results were presented for each exposure scenario and for the aggregated total exposures. Inhalation of indoor air was the highest exposure route for all age groups except nursing infants of occupationally exposed mothers, who had higher exposures from ingestion of breast milk.

The panel discussed a number of issues related to the exposure assessment. Some panelists said the report should have gone further to identify sources and scenarios of potentially high toluene exposures, and several members suggested additional exposure sources that might have been included. Regarding consumer exposures, several panelists expressed concern with the assumption that product usage instructions would be followed. The use of a 95<sup>th</sup> percentile for high-end exposure parameters was questioned by several members, and the panel discussed whether individuals with exposures greater than the 95<sup>th</sup> percentile should be considered. Some panel members questioned whether the values presented were adequate to bound a screening exposure assessment, and one suggested a probabilistic approach be used.

The sponsor presentation of the risk characterization described two different approaches used to assess potential health risk. The first approach calculated hazard quotients and indices based upon *externally administered* toluene doses. The second approach used PBPK modeling to estimate *internal toluene blood concentrations*. The presenter explained how the second approach incorporated temporal exposures, integrated multiple exposure routes, and captured age-dependent ADME (absorption, distribution, metabolism, and excretion) changes. The presenter explained the age-specific PBPK models employed by the second approach and compared the values obtained from the modeling with the exposure scenario estimates, and also with available biomonitoring data on children. He noted that both the internal and external dose approaches result in hazard indices less than one.

Much of the panel discussion of risk characterization focused on the PBPK modeling approach. Many panelists thought the approach valid and encouraged its use. The panel discussed strengths and limitations of the approach and suggested that the authors more fully describe its assumptions and uncertainties. Some panel members questioned the appropriateness of using the Acute Exposure Guideline Level (AEG-1) for a toxicity benchmark in the risk characterization. One panel member noted that hazard index values less than one resulting from either of the two approaches might not demonstrate safety because the critical endpoint for toluene neurotoxicity in the infant brain is not known. The panel discussed the issue of exposures to multiple chemicals with similar mechanisms of toxicity and whether a VCCEP assessment should consider other chemical exposures.

Regarding data needs, the sponsors summarized the hazard and exposure data presented in the report and concluded that these data were adequate. They did not identify any data needs for the hazard or the exposure assessments.

The panelists discussed both data needs and data gaps for toluene. Panel members identified a number of data gaps, and two panelists identified data needs. One said the developmental neurotoxicity guideline study (DNT) is a data need because neurotoxicity is the most sensitive effect and there is a supposition made that the adult values will protect children. Another said a further analysis of the existing developmental neurotoxicity animal studies should be done to evaluate the need for a DNT guideline study and PBPK modeling should be conducted. Most panelists identified one or more data gaps for toluene. The areas of greatest concern were neurotoxicity and immunotoxicity in young age groups, cumulative exposures to multiple chemicals, and the high degrees of uncertainty in many exposure

scenarios. Data gaps in the areas of epidemiology, PBPK modeling, and several other areas also were identified and discussed.

Several panel members identified what they regarded as *general data needs* that apply not only to toluene but also to other VCCEP chemicals. They noted that more information and a better understanding in these areas would improve the children's risk characterization for many chemicals. In the hazard area, one panel member identified two general needs: (1) conduct more juvenile assessments to gain a better understanding of how to interpret and identify toxicity end points and make comparisons among species, and (2) obtain a thorough understanding of the effects of early life exposures on adult disease status and health effects. In the exposure area, several panel members identified the need to better understand how people really use consumer products and how children are involved in their uses. Panel members noted that better data and understanding of these exposures would particularly affect the high-end exposure estimates. One panel member suggested validation of at least some of the residential exposure scenarios.

## 1. Participants

### Sponsor

American Chemistry Council Benzene, Toluene, and Xylenes VCCEP Consortium (BP, Chevron Phillips Chemical Company LP, E.I. du Pont de Nemours & Company, ExxonMobil Chemical Company, Flint Hills Resources, LP, Marathon Petroleum LLC, Shell Chemical LP, Sterling Chemical Company, Sunoco, Inc., and Total Petrochemicals U.S.A.)

### Presenters

John Bukowski, Ph.D. Epidemiology  
WordsWorld Consulting

Sean Hays, M.S. Physiology and Chemical Engineering  
President, Summit Toxicology, LLP

Andrew Jaques, M.P.H. Environmental and Occupational Health  
American Chemistry Council Benzene, Toluene, and Xylenes VCCEP  
Consortium Manager

Julie Panko, B.S. Industrial Hygiene  
Managing Health Scientist, ChemRisk

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Toxicology Consultant, C&C

### Peer Consultation Panel Members<sup>1</sup>

Michael Bates, Ph.D. Epidemiology  
University of California, Berkeley

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U.S. EPA, National Health and Environmental Effects Research Laboratory

Gary Burlison, Ph.D. Viral Immunology  
BRT-Burlison Research Technologies, Inc.

John DeSesso, Ph.D. Anatomy and Teratology, DABFE, DABFM  
Mitretek Systems

Michael L. Dourson, Ph.D. Toxicology, DABT  
Toxicology Excellence for Risk Assessment (*TERA*)  
(Panel Chair)

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<sup>1</sup> Panel members served as individuals on this panel, representing their own personal scientific opinions. They did not represent their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent the opinions of their employers or those with whom they are affiliated.

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U.S. EPA, National Center for Computational Toxicology

Sam Kacew, Ph.D. Pharmacology  
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Chad Sandusky, Ph.D. Pharmacology  
Physicians Committee for Responsible Medicine

Donna Vorhees, Sc.D. Environmental Health  
Menzie-Cura & Associates, Inc

Clifford Weisel, Ph.D. Chemical Oceanography  
Robert Wood Johnson Medical School / University of Medicine and Dentistry of New Jersey

## **Observers and Other Attendees**

A list of observers and other attendees is found in Appendix A.

## **2. Background**

This peer consultation meeting was organized by Toxicology Excellence for Risk Assessment (*TERA*). *TERA* is an independent non-profit organization with a mission to protect public health through the best use of toxicity and exposure information in the development of human health risk assessments. *TERA* has organized and conducted peer review and peer consultation meetings for private and public sponsors since 1996. Under this program, *TERA* is organizing peer consultation meetings for assessments developed as a part of the Voluntary Children's Chemical Evaluation Program (VCCEP). The toluene assessment was submitted by the American Chemistry Council Benzene, Toluene, and Xylenes VCCEP Consortium (BP, Chevron Phillips Chemical Company LP, E.I. du Pont de Nemours & Company, ExxonMobil Chemical Company, Flint Hills Resources, LP, Marathon Petroleum LLC, Shell Chemical LP, Sterling Chemical, Sunoco, Inc., and Total Petrochemicals U.S.A.).

The VCCEP program is a voluntary pilot program and part of the U.S. Environmental Protection Agency's (EPA) Chemical Right-to-Know Initiative (<http://www.epa.gov/chemrtk/vccep/index.htm>). The goal of the VCCEP is to enable the public to understand better the potential health risk to children associated with certain chemical exposures. The key question of the program is whether the potential hazards, exposures, and risks to children have been adequately characterized, and, if not, what additional data are necessary. The EPA asked companies that manufacture and/or import 23 chemicals (that have been found in human tissues and the environment in various monitoring programs) to volunteer to sponsor chemical evaluations in a pilot program. Sponsorship requires the companies to collect or develop health effects and exposure information on their chemicals and then to integrate that information in a risk characterization assessment and a data needs assessment.

The VCCEP pilot program was designed to use a tiered testing approach. For toxicity data, specific types of studies have been assigned to one of three tiers. For exposure data, the depth of exposure information increases with each tier. Tier 1 hazard assessments use all available data, and therefore some of the Tier 1 chemical assessments will include toxicity studies indicated for Tiers 2 or 3. The Benzene, Toluene, and Xylenes VCCEP Consortium volunteered to sponsor a Tier 1 assessment for toluene. Links to the submission document and appendices are available to the public on the Internet at <http://www.tera.org/peer/VCCEP/Toluene/TolueneWelcome.html>. If data needs are identified through this process, the Benzene, Toluene, and Xylenes VCCEP Consortium will decide whether to volunteer for any additional data generation or testing and whether to provide a Tier 2 assessment for VCCEP peer consultation.

To provide wide-ranging scientific review of the sponsor's assessment, each submission undergoes review and discussion by a peer consultation panel in an open meeting with the public invited to observe. The purpose of the meeting is to provide a science-based peer consultation on the data needs for the chemical, utilizing the assessment submitted by the sponsor, as well as the expertise and knowledge of the panel.

The VCCEP Peer Consultation Panel for the toluene submission consisted of 12 members independently selected by *TERA*. Each panel member disclosed information regarding potential conflicts of interest and biases for the VCCEP program in general, for toluene specifically, and for the Benzene, Toluene, and Xylenes VCCEP Consortium (its member companies and submission authors). *TERA* evaluated these disclosures in selecting the panel members. The disclosures were publicly presented at the beginning of the meeting (see Appendix B for the panelist disclosure statements). The panel members have experience in various disciplines, including toxicity testing, exposure evaluation, risk assessment and management, toxicology, and children's health. The panel received a copy of the submission and key references approximately one month before the meeting, so that they had adequate time to review the documents and prepare for the discussions. Panel members bring a range of views and perspectives to the peer consultations, reflecting the interest in VCCEP by a wide range of stakeholders. The panel does not attempt to reach consensus, rather the individual opinions of the members are noted. Panel members serve as *individuals*, representing their own personal scientific opinions. They do not serve as representatives of their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent the opinions of their employers or those with whom they are affiliated.

Members of the public were invited to observe the panel discussions by attending the peer consultation meeting or by viewing a live web cast of it. They were also given the opportunity to provide brief oral and written technical comments on the assessment document for the panel's consideration.

*TERA* prepared this meeting report. The report summarizes the sponsors' presentations, the panel discussions, the sponsors' comments during the discussions, and comments from the public. The meeting report is a summary, not a transcript. Individual opinions of the panel members are noted (although panelists are not identified by name), along with areas of agreement and disagreement. Panel members have reviewed and commented on the draft report and their comments have been incorporated. The sponsors also were given the opportunity to review the draft report to confirm the accuracy of their presentations and remarks. This report is available on the Internet at <http://www.tera.org/peer/VCCEP/Toluene/TolueneWelcome.html>.

This report is organized into sections corresponding to the submission's hazard assessment, exposure assessment, risk characterization, and data needs sections. Issues and concerns raised during the panel discussions did not always lead to recommendations for additional studies or data gathering. The

recommendations of the panel members regarding the need, or lack of need, for additional data apply only to the VCCEP program.

### **3. Introductions, Conflict of Interest, and Meeting Process**

The meeting opened with a welcome by Ms. Jacqueline Patterson of *TERA*. She described the background and purpose of the VCCEP and the agenda for the meeting. Ms. Patterson noted that copies of panel members' biographical sketches and conflict of interest (COI) and bias disclosure statements were provided to all attendees (see Appendix B). All the panel members then introduced themselves and noted whether they had additions or changes in their disclosure statements. No members had changes or additions.

Dr. Dourson, the panel chair, described how the meeting would be run. He explained that discussions would be based on the items found in the Charge to the Panel (located in Appendix B). He noted that all panelists would have the opportunity to state their own positions on the charge items and to ask one another clarifying questions and further discuss the issues. No attempt would be made to reach consensus positions on the charge items. The chair reminded the panel that the purpose of the peer consultation is not to critique the submission document *per se*, but to answer questions on data adequacy for characterizing risk to children.

### **4. Sponsor Introduction**

Mr. Andrew Jaques of the American Chemistry Council identified the companies in the Benzene, Toluene, and Xylenes VCCEP Consortium that were sponsors of the toluene submission. These include BP, Chevron Phillips Chemical Company LP, E.I. du Pont de Nemours & Company, ExxonMobil Chemical Company, Flint Hills Resources, LP, Marathon Petroleum LLC, Shell Chemical LP, Sterling Chemical, Sunoco, Inc., Total Petrochemicals U.S.A., and additional support was provided by the American Petroleum Institute. He outlined the presentations to be given during the meeting, discussed the reasons that toluene had been selected for the VCCEP pilot program, and described toluene's chemistry and the applicable governmental regulations. See Appendix C for Mr. Jaques presentation slides, which provide further details.

### **5. Hazard Assessment**

#### **5.1 Sponsor Presentations**

##### **5.1.1 Animal Toxicology**

Dr. Ceinwen Schreiner of C&C Consulting summarized the hazard data from the *in vitro* assays and from the studies on animals that were contained in the sponsor's submitted assessment (see Appendix C for her presentation slides, which provide further details). After stating that toxicity data are available on toluene to address all of the VCCEP hazard endpoints, she summarized the Tier 1, 2, and 3 studies that have been conducted.

Dr. Schreiner presented results from studies on genetic toxicity, developmental toxicity, reproductive toxicity (including a 2-generation inhalation test), transplacental absorption, and male fertility. She also

described the hazard data available on immunotoxicity, toxicokinetics and metabolism, neurotoxicity, and carcinogenicity.

Dr. Schreiner concluded that based upon animal studies the most sensitive endpoint for toluene hazard and risk assessment was neurotoxicity. This effect was expressed as neuromuscular effects and impairment of sensory functions. Toluene produced both developmental and postnatal neurotoxicity. Toluene also showed developmental toxicity expressed as low birth weights and delayed ossification, which occurred primarily at maternally toxic levels. Reproductive performance and fertility were not affected by toluene. The chemical was non-genotoxic and non-carcinogenic in animal studies, and it was classified as “not identifiable as a human carcinogen” by IARC (International Agency for Research on Cancer). Immunotoxicity was an inconsistent finding indicated in some studies, but this endpoint was less sensitive than neurotoxicity.

### ***5.1.2 Epidemiology***

Dr. John Bukowski of WordsWorld Consulting summarized the human data in the toluene submission (see Appendix C for his presentation slides, which provide further details). He presented both epidemiology studies and case reports.

Regarding human reproductive effects, Dr. Bukowski described the evidence available for spontaneous abortions from occupational exposures to toluene. He also discussed the association between toluene exposure and infertility, stating that the association was to maternal (not paternal) exposures. He said the data supporting this association were limited and included substantial problems caused by selection bias and other factors. He also noted individual case reports, which suggested that women experiencing high toluene exposures during pregnancy might experience symptoms similar to fetal alcohol syndrome. Regarding neurological effects, Dr. Bukowski presented both behavioral and sensory studies, and he discussed their findings and limitations. He noted that the most sensitive endpoint for toluene effects in humans appears to be decreased color discrimination. He concluded by stating there is strong evidence to support toluene’s association with behavioral and sensory neurological changes, both of which appear to be temporary.

## **5.2 Clarifying Questions from the Panel**

Responding to a question about the relationship between durations of exposure and observed effects, Dr. Schreiner said that longer exposure durations did not appear to increase the severity of adverse effects in animals. Dr. Bukowski said the same thing was likely true for humans, although the variation of exposure durations had not been studied directly. He noted that reversibility of effects was often seen when occupational exposures were discontinued, such as over weekends or during vacations.

When asked for clarification on the report by Ng et al. (1992a) that showed an association between occupational exposure to toluene and spontaneous abortions, Dr. Bukowski explained that 70% of the abortions reported in the occupational exposure group occurred in only four women. He noted that spontaneous abortions tend to occur repeatedly in some women, and having such subjects in a study group could inflate the reported values of the group. He said the Ng study sample size was too small to restrict the analysis to first abortions only to attempt to correct for this problem. Dr. Bukowski added that he did not know the normal rate of spontaneous abortions in Singapore where the Ng study was conducted; however, studies from China and Thailand have reported spontaneous abortion rates of 6-8%. Those results suggest that normal Asian populations have rates higher than the 3% reported for the control group in the Ng report.

One panelist asked if the toxic effects of toluene were additive or synergistic to the effects of the xylenes, benzene, or similar solvent chemicals. Dr Schreiner responded that she did not know of any studies demonstrating additive or synergistic effects, but she said toluene at high doses was known to *reduce* the toxicity of benzene (Hsieh et al, 1990b). Another panelist noted that in rats the auditory toxicity of these solvents was additive.

Citing the report of Burns et al. (1994), a panel member said the hazard assessment of immunotoxicity was correct in stating that toluene showed no effect on host resistance following oral exposure to toluene, but it was incorrect in concluding that toluene should not be classified as lacking immunotoxicity. He suggested the hazard assessment document and presentation slides be modified to indicate that toluene demonstrated immunotoxicity in some of the immunotoxicity assessment parameters. The presenter and sponsors responded that a wording modification was acceptable to them to avoid giving the impression that toluene was completely lacking activity in all of the immunotoxicity endpoints. They noted that immunotoxicity did not appear to have had a meaningful impact in the chronic toluene animal studies; however, they acknowledged that long-term human exposures to toluene might be a contributing cause of bronchitis, which is occasionally reported in occupationally exposed workers. The panel member noted that Dr. R. R. Dietert of Cornell University is exploring the impact of an organism's developmental status on immunotoxicological risk and has reported (Dietert et al., 2002) that neonate animals are more sensitive than adults to immunotoxicants. This panelist recommended that the work of Dietert be included in the immunotoxicology section of the toluene submission. He added that the immunotoxicity data were not presented clearly in the report. Specifically, he said Aranyi et al. (1985) demonstrated clear evidence of immunotoxicity following toluene inhalation (page 63 of the toluene report), but page 64 of the report states that "toluene does not significantly adversely affect the immune system." While this statement is true for the oral exposure studies, the statement appears to summarize all of the immunotoxicity studies, and it is not true for the inhalation study by Aranyi et al.

Another panelist said that with so much hazard data existing on toluene, it would be interesting to compare the most important effects noted in animals with those noted in humans. The presenters replied that at high doses toluene's reproductive effects are similar in animals and humans. Toluene's neurological effects are generally comparable at lower doses, with auditory effects occurring in animals and visual color discrimination effects occurring in humans.

A panel member noted that, according to the report and to the presenter, the biases existing in the epidemiology studies all seemed to result in an over-estimation of toluene's risk. She asked if this was really true overall. Dr. Bukowski responded that biases in epidemiology studies can go in either direction and result in a chemical's risk being over- or underestimated; however, in the toluene studies most of the biases did indeed tend toward over-estimating the risk to humans.

Two panelists asked for more information about possible doses received by toluene abusers and how toluene abuse by pregnant women might impact their developing embryos and fetuses, which lack the enzymes to detoxify toluene. The presenters replied that doses received by intentional abusers are not known with any certainty, but the concentrations of toluene contained in bags and similar containers used for intentional inhalation abuse have been estimated at 5000 to 10,000 ppm. They added that toluene inhaled by a pregnant woman would be detoxified to some extent by the woman's enzymes before it crossed the placenta, even though it might not be detoxified by her embryo or fetus.

### **5.3 Panel Discussion of the Hazard Assessment**

The panel discussion of the hazard assessment addressed three charge items, which are summarized in the sections that follow:

1. *Discuss whether the information available on local and systemic toxicity, acute and chronic toxicity, mode of action, and ADME (absorption, distribution, metabolism, and elimination) is adequate to identify and assess potential hazards.*
2. *Discuss whether the hazard data are sufficient to characterize risk for subpopulations, such as a) the prospective parents, b) the embryo and fetus, c) the nursing infant, and d) the post-nursing child through adolescence to the age of sexual maturation.*
3. *Discuss any other issues related to the toluene hazard assessment.*

### **5.3.1 Information to Identify and Assess Hazards**

A panelist began the discussion by noting the large amount of hazard information available on toluene. He said a clear distinction exists between the adult and neonate responses and this likely is due in large part to metabolic differences. Neonates of all species have little or none of the CYP2E1 enzyme activity needed to detoxify toluene; therefore, neonates are more at risk than adults. He thought this was an important consideration that should have been discussed in greater detail in the hazard assessment. A panelist added that in humans CYP2E1 activity does not develop until 6 to 12 months of age, but he did not know the age at which it develops in laboratory animals.

Another panel member commented on Table 6.8 in the toluene report (pages 75-76), which lists several rat inhalation studies. Although the test conditions were not identical among the studies, he noted that rat pups exposed only during the postnatal period (Slomianka et al., 1990, 1992) showed a lower NOAEL than pups exposed prenatally (Ono et al., 1995; Thiel and Chahoud, 1997; Hougaard et al., 1999). He thought the differences in NOAELs reported in these studies might possibly reflect differences in metabolic capability, but, alternatively, they might reflect differences in tissue susceptibility as the organism develops. Another panelist stated that dosing dams was far different than dosing rat pups directly, but he reminded the panel of the great difference between rodents and humans in the degree of brain development at the time of birth. He advised caution in using the hippocampal effects reported in rats (Slomianka et al., 1990, 1992) for human risk assessment.

Other panelists discussed whether peak blood level or area-under-the-concentration x time curve (AUC) blood level was more important in assessing thresholds for rodent and human neurotoxicity. The panel did not resolve this question, but they did conclude that peak blood levels were likely to be important during toluene abuse situations, especially if the abusers were pregnant women.

The panel also discussed the windows of vulnerability that exist during development. They said the windows occur at different fetal/neonate ages and last for varying durations, depending on both the species and the organ system. They thought that for most types of toxicity the windows of vulnerability would last longer in humans than in rodents. Importantly, the windows of vulnerability for some effects might occur *before* birth in humans and *after* birth in rodents, while for other effects the order might be reversed. The degree of certainty on this issue led one panelist to wonder if it was possible to identify an age range when a human was likely to be most vulnerable to toluene toxicity. Another member wondered whether the panel had sufficient scientific understanding to include a discussion of the windows of vulnerability to toluene's hazards. She said this issue would be important when the panel moved on to discuss toluene's exposure assessment later in the meeting.

Turning to the epidemiology studies and the other human data on toluene effects, a panelist commented on Table 6.13 of the report and its accompanying text (pages 91-97). He said that many human studies exist on toluene, but the overall human database contained substantial weaknesses, as had been correctly noted by the presenter. Dr. Bukowski responded that most of the human studies utilized relatively small

samplings with no real attempts at random selection or the establishment of unbiased sampling frames. He said the apparent selection bias in the available literature is understandable, but it does create a weakness in the overall human data set. The panelist added that the studies often appeared to have been designed without the input of an epidemiologist. He concluded the epidemiology data were “patchy at best”, even though a large number of studies existed. Another panelist said the workplace studies shown in Figure 2 of the U.S. EPA IRIS Toluene Toxicology Review (EPA, 2005) showed that inhalation exposures above 50 ppm were generally positive, while exposures less than 30 ppm were generally negative. He said although each individual study could be criticized, the trend was clear when a weight of evidence approach was used to evaluate the human occupational data. Another panel member noted that Table 6.14 of the sponsor’s report (page 96) summarized neurobehavioral/psychometric tests among toluene-exposed workers. He said most of the studies in the table were of small size; therefore, the threshold that appears to exist at 50 ppm may not be real. He suggested the report add a caveat noting this possible limitation.

Other members of the panel discussed concerns on a variety of hazard-related issues. One noted the lack of epidemiology data available on chronic, low-level exposures, and he wondered if such exposures might affect children’s health. Another said most hazard data presented in the report were on combinations of toluene and other solvent chemicals, rather than on toluene alone. One recommended further explanation of Table 6.10 (page 82) and an expansion of the table to compare the skin permeability between children and adults. Another was concerned that the overall hazard assessment presentation implied that the neurological effects observed from toluene exposure were reversible. He cautioned that intentional abusers of toluene who expose themselves to high doses might be doing irreversible damage to themselves, or in the case of pregnant women, to the developing nervous systems of their fetuses.

### ***5.3.2 Hazard Data on Subpopulations***

One panel member said several well-conducted studies were available on sexually mature animals and for *in utero* exposures. Some members cited Table 6.5 of the report (pages 60-62) and discussed whether the toluene database was weak on the subpopulations of nursing infants through adolescents. They thought the 2-generation study (API, 1985) might provide important information on neonates if certain additional details of the study were known. They wanted to know if the pups were able to lick the fur of the dams and if the pups were present in the inhalation chamber. They thought this information would indicate whether the pups received direct exposure to toluene, in addition to their exposure via milk. Dr. Schreiner responded that the dams in the study did not have their fur washed off, so the pups were able to obtain direct oral exposure to toluene by licking the dams’ fur. She said the pups were not exposed to toluene via inhalation until the time of weaning on PND (postnatal day) 21. Another member said it would be possible to apply physiologically based pharmacokinetic (PBPK) models to the studies listed in the hazard tables and generate data on the blood and tissue levels of toluene in developing animals at essentially all time periods. He said that applying these models might provide the information needed to address all of the subpopulations of interest.

Referring to the rat postnatal exposure studies (Slomianka et al, 1990, 1992), a panelist said it was important to realize that although the volumetric changes that occurred in the hippocampus showed recovery, the recovery of volume might simply have been from fluid moving into the hippocampal area. It should not be assumed that recovery of normal hippocampal function had occurred. Another panelist added that the studies of Ono et al. (1995) and Hougaard et al. (1999) both showed learning defects demonstrated by decreased water maze performance. He said these learning defects suggest hippocampal impairment.

Another panelist noted that the term “stress-related” was used several times in the hazard assessment to explain various adverse effects observed in the toluene studies. He asked if these adverse effects really

were related to stress, or if they were instead caused by the chemical toxicity of toluene. Other panel members responded that answer depended on the specific adverse effect in question. They said some types of adverse effects are known to be caused by the stress of experimental testing conditions and are independent of the chemical being tested. For example, stress is known to affect the immune system in both animal experiments and in humans.

Another panelist raised the question of whether the default uncertainty factor of 10 was sufficient for toluene in all the human subpopulations. Dr. Bukowski responded that he knew of no data indicating that an uncertainty factor of greater than 10 was warranted.

### ***5.3.3 Additional Hazard Issues***

In considering toluene hazard issues that had not been addressed previously, one panelist emphasized that effects of toluene in humans that were termed “subclinical” in the report should not be dismissed as unimportant from an overall public health point of view. An example of such an effect is decreased color discrimination. He said the severity of such an effect might be assessed by expressing it as equivalent to a certain time period of aging on an individual’s perceptual ability. For the effect of color discrimination, and maybe also for other adverse effects, this panelist thought that longer exposures to toluene would likely lead to more severe or more irreversible effects. He also said that that chronic toluene exposure alters neurotransmitter pathways, and this effect could have irreversible consequences. Another panel member agreed that toluene’s effect on neuronal pathways could be permanent, and he thought that concentrations of toluene as low as the Reference Concentration (RfC) or Reference Dose (RfD) values might present a neurotoxicity hazard. He said pharmacokinetic data on children are needed to address this concern.

One panelist noted that EPA calculated its RfD (EPA, 2005) based on renal effects reported in an NTP study (NTP, 1990). He wondered if long-term oral exposure to toluene might cause renal toxicity, possibly due to a toluene metabolite, and if this effect might be meaningful in the hazard assessment. Another panelist replied that at low level oral dosing the kidney excretes essentially everything, while at higher doses, it does not, and so systemic toxicity certainly might occur.

A panelist noted that toluene is one of many volatile organic compounds that share similar phenotypic expression of acute and developmental toxicity (Bushnell et al, 2005). Toluene and these other chemicals also share many identical target sites on nerve membrane ion channels. He said the similarity of action of these volatile lipophilic substances makes it reasonable to presume that they are acting through essentially identical mechanisms. Therefore, the true risks of exposure to children are likely to be represented by the cumulative exposure to toluene and to all similarly-acting volatile organic compounds, and a cumulative risk assessment that includes all of these substances should be considered.

## 6. Exposure Assessment

### 6.1 Sponsor Presentation

Ms. Julie Panko of ChemRisk summarized the exposure data presented in the sponsor's submitted assessment (see Appendix C for her presentation slides, which include further details). She noted the exposure report assessed the inhalation, ingestion, and dermal routes and used both "typical" (average or mean) and "high-end" (90<sup>th</sup> or 95<sup>th</sup> percentiles) values. The exposures were placed in three groups: background chronic ambient exposures, source-specific chronic exposures, and source-specific short-term episodic/occupational exposures. The exposed population was divided into seven age groups as follows: infants from 0 to 12 months old were divided into three groups, children from 1 to 18 years old were divided into three groups, and 19 to 35 year old women were placed in a single group called "prospective mothers." The exposure data were obtained from government databases, published literature, and company data of consortium members. The exposure sources that were considered in the assessment included occupational exposures, ambient outdoor air, indoor air in residences and schools, ingested foods and beverages, product-use exposures, and human breast milk. Exposures to specific sources were presented using scenarios involving gasoline, tobacco smoke, and several types of consumer products.

Ms. Panko presented the results of toluene exposures from each of the individual sources and described the modeling assumptions used in the scenarios of the source-specific exposures. She then presented the aggregated results, which converted all exposure values to the common unit of average daily dose expressed as mg/kg-day. For all age groups, except nursing infants of occupationally exposed mothers, inhalation of indoor air was the primary exposure route. For nursing infants of occupationally exposed mothers, ingestion of human milk was the primary exposure route, followed by inhalation of indoor air. No child-specific exposure sources or scenarios were identified except the ingestion of human milk from occupationally exposed mothers.

### 6.2 Clarifying Questions from the Panel

Responding to a panelist question, Ms. Panko said greater than 95 percent of the water samples and less than 50 percent of the air samples contained non-detectable concentrations of toluene. The 90<sup>th</sup> and 95<sup>th</sup> percentiles used for the high-end values were for the entire United States population.

One panel member asked how the exposure of a nursing infant of an occupationally exposed mother would be impacted if the mother *did not* express her milk or nurse throughout the workday. Mr. Sean Hays, one of the presenters for the sponsors, responded that the toluene in the body of the mother would be rapidly metabolized; therefore, the amount of toluene in the milk received by the nursing infant would be lower if the mother expressed her milk or nursed before or after her occupational exposure during the workday. The amount of the decrease would depend on the length of time between the mother's occupational exposure and the event of her nursing or expressing her milk.

Another panelist commented on the databases the sponsors had consulted to obtain information on the toluene content of consumer products. He noted that some brands of nail polish contain up to 40% toluene, which is much greater than the figures for nail polish listed in general product databases used by the sponsors. He said employees of nail polish salons that use these high-toluene nail polish products might have high exposures to toluene, and he thought that a scenario describing such usage should have been included in the report. Ms. Panko replied that such a scenario had been considered, but the authors had determined that total toluene exposures of salon employees would not be greater than exposures occurring in other scenarios that the report presented.

One panelist had several comments on the exposure assessment. He said the report used the term “ambient” air for both indoor and outdoor air, but the term should be used only in reference to *outdoor* air. He also said it was incorrect to assume that “fence line” air concentrations are always high-end concentrations because the key factor is where the toluene air plume touches the ground, and this might occur beyond the fence line. He added that the RIOPA (Relationship between Indoor, Outdoor, and Personal Air) study cited on page 116 of the report is not necessarily a good study to use for determining the highest stationary sources of toluene emissions, and it might contain better information on mobile sources of toluene than on stationary sources. The panelist also said it was incorrect to assume that users of consumer products follow directions on the product labels.

Another panelist asked for the basis of the statement, which was made throughout the exposure presentation, that “conservative assumptions” were used in the exposure modeling. Ms. Panko noted that many exposure scenarios did not provide information on room sizes, ventilation rates, etc., and that, in these instances, the authors made assumptions for these parameters that they considered to be conservative. Mr. Jaques added that biomonitoring data of toluene in blood and milk, in the few instances where these data were available, supported the assertion that the exposure models had made conservative assumptions. One panel member disagreed that biomonitoring data indicated that conservative exposure assumptions had been used in the report since the time frame between any exposures and when the biological sample was taken is not known.

### **6.3 Panel Discussion of the Exposure Assessment**

The panel discussion on Exposure Assessment addressed the following seven charge items, as well as other issues and comments raised by panel members.

4. *Discuss whether the fate of toluene is adequately understood, both in the environment and within the human body.*
5. *Are the potential sources of toluene exposure adequately identified? Are there other sources that should have been considered?*
6. *Discuss whether the available data are adequate regarding the following exposure aspects: sources, routes, frequency, duration, and intensity.*
7. *Were the data, exposure scenarios, age groupings, parameters, and assumptions used in the exposure assessment appropriate to characterize risk to children? Should other data or scenarios have been evaluated or different assumptions used?*
8. *Discuss whether the exposure data are sufficient to assess subpopulations, such as a) the prospective parents, b) the embryo and fetus, c) the nursing infant, and d) the post-nursing child through adolescence to the age of sexual maturation.*
9. *Discuss whether the estimates of exposure are defensible and have been calculated correctly.*
10. *Discuss any other issues related to the toluene exposure assessment.*

### **6.3.1 Fate of Toluene**

A panel member said the fate of toluene is well understood both in the environment and in the human body. No other panelists had any additional items to discuss for this charge item, and several stated their agreement that the fate of toluene was adequately understood.

### **6.3.2 Sources of Toluene Exposure**

Regarding toluene sources, a panelist recommended the sponsors search beyond the general consumer product survey databases to find additional data on the toluene content of products. For example, he mentioned that OPI Products, Inc. is a manufacturer of cosmetic nail products that are high in toluene. Information on the toluene content of their products can be obtained by contacting the company directly. The same is likely true for many other companies that manufacture toluene-containing products. This panelist also said the report might have included additional sources such as incense and the interiors of new cars, but he acknowledged it is a judgment call on how comprehensive the exposure section of the report should be.

Another panel member said the report did not adequately cover the scenario of refueling a passenger car while car windows are open and an infant is sitting in a rear car seat. This panelist also questioned cutting off high-end exposures at the 95<sup>th</sup> percentile. He said the upper 1% of children in the United States numbers about 200,000, and such a large number should not be dismissed. He wondered whether it might be more appropriate to approach exposure by using modeling to look at the entire spectrum. Another member added that it might be good to use probabilistic approaches for the exposure estimations. She noted that there always seems to be a huge data gap for how people use products and in how much exposure they receive from them. A third panelist responded that a reason for *not* using the very highest exposure values (top 1%) is because of the high degree of uncertainty in these values; there is much less uncertainty at the 90<sup>th</sup> or 95 percentile. She added that the current VCCEP approach of starting with a screening exposure assessment is acceptable as long as the values are adequately bounded. She thought the current approach was preferable to using a probabilistic approach for VCCEP Tier 1 exposures. One panelist observed that the report had successfully bounded the exposure values by including occupationally exposed mothers and their nursing infants, but another member countered that these values were only for short-term exposures and the time periods should be expanded to include the infants post-nursing. Another said the panel really did not know if the exposures had been bounded because of the high degree of uncertainties, such as: how to average exposure times, whether to address differences in schools and industrial areas, and how to dovetail the windows of vulnerability with the windows of exposure. She said the VCCEP's purpose is not to make policy decisions, but to characterize data adequacy.

The Chair, referring to Figure 7.1 of the report (page 113) asked the panel if they thought any potential exposure sources were missing from the report's assessment. Several panel members noted additional items the authors might consider addressing, such as solvent abuse situations, combustion scenarios (forests, leaves, garbage, etc.), walking along heavily traveled roadways, and vapor intrusion into homes located above in-ground plumes.

### **6.3.3 Adequacy of Exposure Data**

A panelist stated the frequency and duration of exposures should be bounded and available data from schools with air quality problems, houses with attached garages, intentional abuse situations, and similar potential high exposure situations should be included. Another added that both peak exposure values and

time weighted averages (TWAs) should be presented. Mr. Hays replied that the peak exposures were captured in the TWAs.

Another member questioned the method used to calculate the indoor-outdoor delta values (page 124). He said the deltas listed in Table 7.6 were from a study with a relatively short time period when high indoor-outdoor air exchange rates occur, i.e., during warm weather when house windows were likely open. He said that higher delta values would result if the measurements had been conducted during a colder season of the year when windows would be closed. Ms. Panko responded that both typical and high-end delta values were presented in the report. The high end deltas were based upon houses with attached garages. She said the delta values presented were reasonable to use for estimating indoor toluene air concentrations, and she cited the study of Shields et al. (1996) as a source of additional details on this subject.

One panelist said exposure assessments conducted by the European Commission routinely factored in the increased ventilation rates resulting from exertion or from pregnancy. He suggested that such factors might be used in this report to refine the exposure assessment. Another member noted that the report contained no discussion of differences in dermal permeability among the age groups and pointed out that the barrier function of the skin was incomplete in premature infants and neonates. Other panelists thought such a discussion was unnecessary for the report because dermal exposure was not a meaningful route for toluene exposure, especially for infants.

#### ***6.3.4 Adequacy of Exposure Scenarios***

One panelist said that overall he did not disagree with the approach the report used to present and discuss the exposure scenarios; however, he emphasized that consumers often do not follow product usage directions and there is a high degree of uncertainty regarding the exposure occurring from any given scenario. Another panelist agreed and also was not satisfied with the way exposure scenarios were addressed in the report. She wanted more information on the use of toluene-containing products by children and also on exposures to children who might be present in high-exposure environments, such as cosmetic nail salons, household rooms with kerosene heaters or where adults were refinishing furniture, and garages where teens were degreasing or repairing car engines. She thought bimodal distributions were likely to occur in many exposure situations, and these events should be identified and discussed in the report. She added that the age groups used in the toluene report (Table 7.1, page 114) do not follow the guidance provided by EPA in its child exposure handbook (EPA 2002c)

#### ***6.3.5 Adequacy of Subpopulation Data***

Panelists had nothing to add to their previous discussions regarding this charge item.

#### ***6.3.6 Accuracy of Calculations***

Ms. Patterson informed the panel that a *TERA* staff member had spot-checked the calculations contained in the report and in its appendices. Overall, the calculations were reproducible, but a few errors were identified and forwarded to the sponsors. Ms. Panko distributed an errata page correcting the errors. She also distributed additional pages of the Household Products Database because some portions of this printout had been inadvertently deleted when copied into the submission document. (Both the errata page and the additional database pages are found in Appendix D of this report.)

Other members noted two additional errors in the report: on page 120, the table should be titled Table 7.4, rather than Table 7.8. On page 132, each of the four values in Table 7.18 in the column headed *Modeled Human Milk Concentration (mg/L)* should be increased by 10-fold.

Referring to Table 8.5 (page 194), one member said it was not clear where to find the basis for the values listed in the Hazard Index column. Because of this, he could not independently confirm whether errors existed in the values presented in the table. He suggested footnotes be added to this table (and to other tables throughout the report) in order to provide the full information needed to reproduce the calculations. He said this would improve transparency of the assessment.

### **6.3.7 Other Exposure Assessment Issues**

No additional issues were identified by the panelists.

## **7. Risk Characterization**

### **7.1 Sponsor Presentation**

Mr. Sean Hays of Summit Toxicology presented the risk characterization assessment (see Appendix C for his presentation slides, which include further details). He summarized the toxicological criteria or benchmarks that were used to compare with exposures, discussed the implications of the existing data on child-specific physiological and metabolic capability, reviewed the different approaches available for assessing potential health risks, and provided the risk assessment results of the differing approaches.

After briefly describing the current EPA IRIS values, Mr. Hays described the two different approaches the assessment used to evaluate the potential health risks of toluene. The first used the common hazard quotient approach by comparing estimated oral doses or inhalation concentrations (time weighted averages) to the RfD or RfC, respectively. They then summed the hazard quotients from different routes of exposure to obtain a hazard index (HI). The second approach used PBPK modeling and *internal toluene blood concentrations*. An HI was calculated by comparing modeled blood levels from identified exposures (all routes of exposure) to the blood levels corresponding to the toxicity benchmarks. Mr. Hays explained that the use of the second approach is possible because toluene's pharmacokinetics are well-understood and because sufficient experimental data exist to allow prediction of blood levels from various exposure regimens. He said use of the second approach is preferable because it evaluates the impact of temporal exposure patterns, integrates exposures from multiple routes, and captures age-dependent changes in ADME. In presenting the age-specific PBPK models, he noted that the children's models provided a rational basis for examining the relative impact of known physiological and metabolic differences between children and adults; however, the children's models were not experimentally validated. He described and explained the implications of the finding that the lower metabolic capability of children versus adults leads to higher toluene blood levels in children from equivalent toluene exposures.

Mr. Hays presented the results from risk assessments using each of the two approaches, noting that the use of either approach results in a hazard index for toluene of less than one ( $HI < 1$ ). He explained that the hazard index values from the administered dose approach (the "first approach") are higher than the corresponding values from the internal dose approach using the PBPK models (the "second approach"). This is because the modeled blood levels reflect distribution of oral and inhalation exposure patterns over the course of the day, based on indoor/outdoor activity and breast-feeding patterns. Mr. Hays also compared the results of the internal dose approach with the exposure scenarios presented in the report,

with the published acute and chronic exposure guidelines, with available health-based benchmarks, and with biomonitoring data available for children. His overall conclusion was that the internal dose approach using PBPK modeling to estimate blood levels is relevant for the human risk assessment of toluene and is likely superior to the administered dose approach. He said use of the internal dose approach shows that toluene exposures from the environment are associated with HIs considerably less than 0.1. The presentation slides in Appendix C provide additional details and explanations for how the PBPK modeling and the hazard indices were calculated, as well as comparing the venous blood concentrations to various exposure guidelines and biomonitoring data from Sexton et al. (2005).

## 7.2 Clarifying Questions from the Panel

Referring to page 189 of the report, a panel member asked about the statement that an air toxic chemical with a hazard index less than 10 would not require further action in terms of a more detailed assessment. Mr. Hays responded that this statement was simply an author's commentary on the text of a published guidance document on risk management (Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997). The statement did not suggest that the sponsors believe chemicals with hazard indices between 1 and 10 do not require further evaluation or action.

## 7.3 Panel Discussion of Risk Characterization

The panel discussion on Risk Characterization addressed three charge items:

11. *Discuss whether the correct benchmarks were used to characterize the chronic and acute adverse health effects of toluene (i.e., RfD, RfC, and AEGL-1).*
12. *Two approaches were used to characterize risk.*
  - a. *The conventional Hazard Quotient (HQ) approach was used to compare exposure estimates to the RfD, RfC, and AEGL-1. Concurrent doses/exposures were summed for a Hazard Index (HI). Is this method appropriate for toluene?*
  - b. *The authors also conducted an alternative, internal dose-based risk assessment. PBPK modeling was used to derive an internal dose metric (e.g., toluene blood concentration profiles and peak rate of metabolism) for the studies underlying the EPA RfD and RfC. They derived age-specific toluene PBPK models for each age group and simulate the exposure assessment(s) to derive internal dose metrics for each exposure scenario and age group combination. They then compared the internal dose metrics for the RfD and RfC to the internal dose metrics associated with the exposure assessment and calculated hazard indices. Is this approach valid? Are the results a defensible characterization of risk for toluene?*
13. *Discuss whether each risk characterization adequately characterizes the risk to subpopulations, such as a) the prospective parents, b) the embryo and fetus, c) the nursing infant, and d) the post-nursing child through adolescence to the age of sexual maturation.*

In response to a request from the panel chair, the panelists first discussed Charge Items 12a and 12b; they then discussed Charge Item 11 and finally Charge Item 13.

### **7.3.1 Comparison of Risk Characterization Approaches**

One panelist expressed a preference for the second approach (PBPK approach). He said the PBPK modeling for children appears to have correctly simulated the clearance, CYP2E1 activity, and other factors in young age groups. Another member of the panel thought the use of PBPK models to estimate the blood levels in children was “enlightening” and provided good insight, but she expressed concern that applying refined PBPK models to screening exposure levels might suggest degrees of certainty, accuracy, and precision that do not exist. The panelist emphasized that the resulting HI values could be no better than their weakest component (the exposure estimate); therefore, she recommended looking at *both* of the risk characterization approaches and considering *both* sets of resulting HI values. Another panelist said he strongly preferred the PBPK modeling approach because it used additional data. He cautioned, however, that the PBPK parameters had not been verified by comparing them to tissue concentrations and the approach assumes that the susceptibility of infant and children’s tissues is the same as that of adults.

One member said he appreciated the sponsors presenting both approaches for the risk characterization. He thought the worst-case HI value of 0.9 obtained from the first approach was a concern, but he was reassured by the lower worst-case HI value obtained from use of the second approach. Another panelist commented that one strength of the PBPK approach was that it attempted to consider an individual’s exposure through an entire time period, while the first approach did not. Other panelists also stated their preference for the PBPK approach over the administered dose approach. The panel members supporting the use of the PBPK approach noted however, that it was vital to fully explain the uncertainties and limitations of the approach in the text. Others discussed the need to avoid a false sense of security from the precision implied by the PBPK model and to remain aware of the uncertainties and assumptions in the estimated exposure values. They recommended that the risk characterization clearly present the precision or lack of precision in its exposure component. One said that using a probabilistic exposure assessment would be a better approach than the current deterministic approach used in the submission but acknowledged that the risk levels might not warrant this level of effort (unlike the benzene evaluation).

Panel members voiced several other concerns. One thought that identifying an HI value less than one is not enough and there must be an understanding of what the HI value *means*. He said that the critical endpoint for neurotoxicity in the infant brain is not known for toluene; therefore, an HI value much less than one still might not demonstrate safety for the developing infant brain. Another thought that the large amount of discussion on the scenario of occupationally exposed, nursing mothers was distracting because it was an extreme example of exposure and drew attention away from more common, more realistic high-exposure scenarios.

### **7.3.2 Benchmarks Characterizing Adverse Health Effects**

A panelist expressed the opinion that the Acute Exposure Guideline Level (AEGL-1) value of 200 ppm, which the report used as the health benchmark for acute toluene exposure, was not appropriate to use for intermittent exposure situations. He also noted that the 8-hour AEGL-1 value of 200 ppm is four times greater than the 8 hr TLV of 50 ppm used in occupational settings. He added that breathing toluene at 200 ppm for 8 hours would impair behavioral performance to an extent greater than the equivalent of legal ethanol intoxication. He said the EPA Office of Air Quality Planning and Standards lists several alternate acute guideline values that would be more appropriate. He added that the acute health benchmark selected should be duration adjusted using the PBPK model on the basis of equal target tissue concentrations.

Two panel members said the RfC was a good departure point for a risk characterization of the chronic health effects of toluene and was clearly better than the RfD because it is based on a more relevant critical

effect for humans. They said that use of the RfC value based on neurotoxicity endpoints would protect against renal toxicity (basis for the RfD) and suggested that this point be made more clearly in the report.

### **7.3.3 Characterizing Risk to Subpopulations**

In discussing this charge item, one panel member stated that *both* of the risk characterization approaches adequately characterized the risk to the indicated subpopulations. However, he said that extreme exposure situations such as intentional abuse were not addressed. Another panelist noted that the subpopulation of 19 to 35 year olds was included in Table 8.4 (page 193) but not in Table 8.5 (page 194). The sponsors agreed that adding this age group to Table 8.5 would make the table more complete by including the subpopulations of prospective parents and of workers in various high-exposure occupational situations. Occupationally exposed nursing mothers also would be included. Panelists noted that additional high-exposure occupational scenarios might be added to Table 8.5. Ms. Panko responded that much of this information is contained in Tables 7.40 and 7.41 (page 157), and she pointed out that these tables applied time weighted averaging to the exposure events.

The panel chair asked if any of the panelists could identify realistic scenarios for any of the subpopulations that would result in hazard indices greater than one. No such scenarios were identified by any of the panel members.

## **8. Data Needs**

### **8.1 Sponsor Presentation**

Mr. Andrew Jaques, the ACC Benzene, Toluene, and Xylenes VCCEP Consortium Manager, summarized the data needs assessment from the sponsors' submission. Regarding the hazard assessment, he said non-human studies are available for each of the VCCEP endpoints. In addition, a large amount of human data is available from epidemiology work and from case studies. Pharmacokinetic data and PBPK models also are available. No toxicology data needs were identified by the sponsors. Regarding the exposure assessment, Mr. Jaques said inhalation of indoor air is known to be the predominant route of exposure, and ample peer-reviewed measurements of air concentrations in homes, schools, and other indoor and outdoor location are available. Additional exposure information is not likely to enhance the risk assessment or to identify new critical exposures or pathways. No exposure data needs were identified by the sponsors.

### **8.2 Clarifying Questions from the Panel**

None of the panel members asked clarifying questions.

### **8.3 Panel Discussion of Data Needs and Gaps**

The panel discussion on the Data Needs Assessment addressed two charge items:

- 14. Identify any additional hazard information that is needed and discuss why it is necessary. Differentiate between data gaps and data needs. Focus on those studies indicated for the next VCCEP tier.*

15. *Identify any additional exposure data or analyses that are needed and discuss why this information is necessary for the next VCCEP tier. Differentiate between data gaps and data needs.*

The individual panelists discussed items that they considered to be data gaps and data needs. The panel chair explained that in the context of the VCCEP pilot program, *data gaps* are defined as areas that could benefit from additional data, additional studies, additional analysis, or clearer presentation. *Data needs* are defined as data gaps *requiring* additional work before the potential risk to children can be adequately characterized. Not all data gaps will be considered data needs, and the panelists may consider the risk characterization results when determining whether a *data gap* is a *data need*.

Five panel members did not identify any exposure or hazard data needs; however, each identified at least one data gap. Four others identified data needs that were of a general nature and not specific to toluene. Several general data needs and gaps were identified by panel members; that is, these are data needs or gaps that apply to toluene but also apply to many other chemicals. Two panelists identified single data needs.

As noted by the section headings, the following text first describes the hazard and exposure data needs/gaps *identified specifically for toluene*, followed by *general* hazard and exposure data needs/gaps that apply not only to toluene but also to other VCCEP chemicals.

### **8.3.1 Hazard Data Needs and Gaps for Toluene**

Panel members identified several data needs and a number of data gaps regarding hazard and toxicity specifically for toluene. Areas of greatest concern were neurotoxicity and immunotoxicity in juveniles. Epidemiology and PBPK gaps were also discussed.

A number of panel members were concerned regarding the adequacy of data on neurotoxicity endpoints in young animals and children. Panel members identified weaknesses in the available data including that the studies tested only high single doses and are not dose-response studies, and that no NOAELs have been established. They also noted that the effect on the hippocampus is not known and data on critical periods of development for neurotoxicity is lacking.

Most of these panel members considered further studies of developmental neurotoxicity as a data gap, but one panel member identified the developmental neurotoxicity (DNT) study listed in the Health Effects Test Guidelines (EPA OPPTS 870.6300, 1998) as a data need for toluene. The panel member noted that neurotoxicity is the most sensitive effect and there is a supposition being made that the adult values will protect children; but it is not known if adult data apply to children for these effects. He agreed with the submission document statement that the available data are insufficient to establish a NOAEL for developmental neurotoxicity and noted that the EPA IRIS file applies an intra-species UF of 10 for the RfC, largely to account for this missing information. However, he noted that current studies on developmental testing do not incorporate a sufficient dose range and do not provide a comprehensive assessment of potential neurotoxic outcomes. Adult testing and occupational epidemiology studies are plentiful and indicate a NOAEL in the range of 34 ppm in the workplace. Available evidence suggests that developmental toxicity in animals occurs at dose levels of around 1000 ppm, but the lower end of the dose response range has not been systematically evaluated with an adequate methodological approach. There is a lack of dose response data in the available studies. The contention that the adult RfC with a 10-fold uncertainty factor will be sufficient to protect against developmental toxicity is speculation in the absence of data, in this panel member's opinion. Therefore, the lack of a DNT guideline study is a data need and should be done in order to document adequately that the potential risks to children have been assessed.

In response to a panel member's question of what NOAEL and LOAEL values would be required from a DNT study to alter the risk assessment as now presented, a panelist said the study results would have to demonstrate a NOAEL below 30 ppm and a LOAEL below 100 ppm. Another panel member noted that he is not sure what the hippocampus results (Slomianka et al. 1990, 1992) mean, and further research may find more subtle effects.

Another panel member suggested that additional data analysis would be helpful to evaluate the need for a DNT. He thought the developmental neurotoxicity animal studies listed in Table 6.8 should be further analyzed (in particular the studies by Slomianka et al.), and PBPK modeling should be conducted to compare the blood concentrations of the pup/fetus in these studies to the adult value at the human based RfC level. He noted that a cursory analysis of the Slomianka data, based on information summarized in the submission, indicate rat post-natal results (volumetric changes in the hippocampus) that would be equivalent to a NOAEL of 50 ppm in humans for continuous exposure. He further noted that applying an additional UF of 3 for database insufficiencies, a value not used by EPA, would still yield a concentration that is slightly above the NOAEL<sub>HEC</sub>, which is the starting point of the RfC determination. Therefore, he recommended that a DNT study not be conducted without a more thorough prior comparison of PBPK values between the pup/fetus and adult levels.

Two panel members pointed out that rat and human brains develop at different times, so using data from Table 6.8 in PBPK modeling may not answer the question of potential effects in humans. They noted that results from a DNT in rodents may have the same difficulty. Another panel member cautioned that that the different effects and behaviors seen in these studies are governed by different brain regions and there is not uniformity in susceptibility to developmental insult. The panelist noted that the specific tests included in the DNT study are not included in the studies listed in Table 6.8 and that this table's studies will provide a hodge-podge, rather than a single paradigm. The original panel member suggesting this analysis asked the other panel member who identified a DNT as a data need whether he would still think the DNT was needed if all the modeled animal blood levels (at the NOAEL) were ten times higher than the human RfC levels. The panel member responded that he agreed this analysis would be useful and he would like to see the data arrayed along the lines of what was done for the epidemiology studies' NOAELs shown for the IRIS RfC. He agreed it would be useful to do this prior to deciding on the need for a DNT. A third panel member agreed that conducting this analysis was a good idea, but he identified it as a data gap.

Immunotoxicity was another area identified as having data gaps. A panel member thought there were data gaps with regard to immunotoxicity data and understanding, but did not think additional immunotoxicity studies were a data need. The study of Aranyi et al (1985) cited in the report showed increased mortality after inhalation exposure to toluene in a Streptococcus host resistance mortality model. However, the mortality data was variable and the panel member outlined the results of a number of immunotoxicity studies in the 1980s and 1990s showing a high degree of variability in mortality studies. Bacterial clearance host resistance assays show less variability. Inhalation studies using bacterial clearance rather than mortality would be a logical next step to understand potential immunotoxicity. In addition, this panel member also identified developmental immunotoxicity as a data gap, and suggested that further investigation of the published data by Dietert et al. that show neonates are more sensitive to immunotoxicants than adults.

Individual panel members identified a number of other areas as data gaps. These include the following: it is not known how the CYP2E1 enzyme develops in the embryo and fetus, the toxicity endpoint in the developing child needs better understanding, and the mechanism of action of toluene on developmental toxicity is unknown, especially relative to ethanol and development of Fetal Alcohol Syndrome (FAS). A panelist commented that even with all the work on ethanol, we still lack a clear understanding of the

ethanol-induced mechanisms that underlie the pathogenesis of FAS, and this will likely be a gap for a long time. Another panel member questioned the submission's statement that most effects are "reversible," particularly whether these effects are reversible for chronic exposures.

In the area of epidemiology, a panel member noted a gap in that the submission is missing a summary of human carcinogenicity studies in the Human Experience section. The same panelist also pointed out that the existing epidemiological studies are small cross-sectional studies. He identified a data gap of an epidemiological cohort study of a toluene exposed population to better characterize the exposure-response relationship. The study should have a good exposure assessment, at least neuropsychological and color vision end points, a sufficient number of participants based on appropriate statistical power calculations (including sufficient non-exposed participants), and a high rate of follow-up of the cohort.

Most panelists thought the PBPK modeling that was done for this submission was useful. Some panel members identified additional work that could be done in this area as data gaps. One panel member thought that the authors should present the PBPK modeling as the primary approach. Two noted that the authors should more fully characterize the weaknesses and uncertainties in the PBPK modeling approach used, so that the reader has a better perspective when comparing it the traditional hazard index approach. Another panel member identified *in vitro* microsomal metabolism studies to calculate Michaelis-Menten kinetic constants in maturing rats at different ages as data gaps. He also saw a gap for *in vivo* kinetic dosing studies with maturing rats to determine clearance. Panel members also noted gaps for the pharmacodynamic component, which could complement the kinetics. One panel member noted a gap of experiments in maturing and adult rats to evaluate neurotoxicity by inhaled toluene and another identified a gap regarding data on sensitivity of the target tissue dose for development. Another panel member saw a data gap with the lack of data to evaluate the performance of the PBPK model in children, but he acknowledged that these data will not ever be available. A general PBPK modeling gap was also identified – that is the lack of information on some physiological parameters in laboratory rats and mice – for example, *in utero* and neonates before PND 11, fetal neonate blood flows, and organ weights.

### **8.3.2 Exposure Data Needs and Gaps for Toluene**

Panel members identified additional data gaps in a number of areas related to exposure assessment and risk characterization of toluene, but did not classify any of these as data needs. Exposure data gaps included cumulative exposure from mixtures of chemicals, peak exposures, identification of high-end exposure, additional exposure scenarios, and the presentation of key information for the risk characterization.

Several panel members identified as a data gap the understanding of toxicity and risk from exposures to mixtures of chemicals with similar modes of action: e.g., toluene together with benzene, xylenes, etc.

Two panel members identified data gaps with regard to peak exposures. One thought that determining whether peak exposures are meaningful under normal uses (as opposed to abuse situations) would be useful. The other said better temporal resolution of exposure data was necessary in order to evaluate the simulations and, in particular, to capture peak exposures.

Two panel members identified data gaps regarding high-end exposures. One thought that the distribution of high-end exposures among subpopulations is not well understood. Another wanted a better description of how the populations of concern are defined. She also wanted some assurance that all the variability in the general population was understood, especially in the population of children. Furthermore, she said that an appropriate risk management choice of percentile to use as "high-end" would be helpful for the entire VCCEP program. For example, if the risk management choice is a 95<sup>th</sup> percentile, then this may

means that up to 5% of the U.S. children are exposed to higher levels of the chemical, and this translates into one million children under age 5 in the U.S.

Several panel members identified data gaps for particular exposure scenarios. One panel member thought that for the mixed media arts scenario, the authors should show all the inputs and identify where each fits within a possible range of values. This scenario should be reanalyzed to quantify the uncertainty in the acute hazard quotient for the infant to gain confidence of the reasonable upper bound on the exposure. Some of the uncertainties to be considered include uncertainties in the PBPK model given the limited data for infants regarding neurotoxicity, uncertainties about product use patterns, and uncertainties in the use of the AEGL-1 as the toxicity benchmark. Another panel member identified two additional scenarios as gaps: (1) commercial nail polish and salons and (2) hobbyists. This panelist suggested confirming with the one manufacturer whether their nail polish still contains toluene and considering relevant exposure to commercial nail polish brands either from home use or within professional salons. The scenario for a nail salon should consider the exposure for both the worker and the worker's child, who might accompany her to work. The hobbyist scenario data gap should reflect people who may spend significant time regularly on their chosen hobby at levels beyond what the mixed media scenario covered. Another panel member noted that there is a data gap regarding exposure in schools, while there is some data, it is a small dataset, and not enough is known.

Several panel members identified gaps with regard to the presentation of the risk characterization. One suggested further analyses of available acute health benchmark values and a thorough discussion of which benchmark would be most appropriate for this application. Two other panel members mentioned additional gaps concerning the hazard index calculations. They thought that the submission should better explain and present the data used to calculate the hazard indices as found in Tables 8.4 and 8.5, so that the reader can easily reproduce the calculations. One panel member thought that the authors should make it more clear in the presentation of the hazard index based on adult blood values (from the PBPK approach) that using adult blood values results in an additional hidden uncertainty factor. This factor should be clarified, and the additional uncertainty regarding the immunotoxicity data should be discussed. He said these two uncertainties tend to balance one another.

A panel member also suggested the authors obtain and evaluate information from Europe, using in particular the European resources that are available for exposure factors and for PBPK models on toluene, benzene, and xylenes.

### ***8.3.3 General Hazard Needs and Gaps***

In the hazard area, one panel member identified two areas as general needs. The first area was a need for more juvenile assessments to better understand how to interpret and identify toxicity end points and make comparisons among species. Another panel member agreed that juvenile toxicity studies are desirable for all chemicals in order to adequately address the VCCEP program needs, but he considered this a data gap, not a data need. The second area identified was a general need for understanding of the effects of early life exposures on adult disease status and health effects; a second panel member noted this same area as a data gap.

### ***8.3.4 General Exposure Needs and Gaps***

In the exposure area, several panel members identified a general need for better understanding of how people really use consumer products and how children are involved in their uses. Data are needed on normal or typical use, not abuse situations. Questions that need further study include: how and when products are used; under what ventilation conditions they are used; whether people read and follow label directions, particularly regarding ventilation; the duration of use; and the quantity used. Panel members

noted that better data and understanding of these exposures would affect the high-end estimates in particular, for toluene and for other chemicals. Panelists noted that there are bits and pieces of information and data available that have been brought to this assessment and others, but that they are not easy to find and not complete. Another panel member suggested validation of at least some of the residential exposure scenarios in order to increase confidence in the resulting exposure estimates.

## 9. References

- Aranyi, C., O'Shea, W.J., Sherwood, .L. et al. 1985. Effects of toluene inhalation on pulmonary host defenses in mice. *Toxicol. Lett.* 25: 103-110.
- Burns, L.A., Bradley, S.G., White, K.L., et al. 1994. Immunotoxicology of mono-nitro-toluene in female B6C3F1 mice. I. Para-nitro-toluene. *Drug Chem. Toxicol.* 17:317-358.
- Bushnell, P.J., Shafer, T.J., Bale, A.S., Boyes, W.K., Simmons, J.E., Eklund, C. and Jackson, T.L. 2005. Developing an exposure-dose-response model for organic solvents: overview and progress on in vitro models and dosimetry. *Environmental Toxicology and Pharmacology*, 19: 607B614.
- Dietert, R.R., Lee, J.E., and Bunn, T.L. 2002. Developmental immunotoxicology: emerging issues. *Hum Exp Toxicol.* 2002 Sep-Oct;21 (9-10): 479-85.
- Environmental Protection Agency (USEPA). 2005. Toxicological Review of Toluene (CAS No. 108-88-3) In Support of Summary Information on the Integrated Risk Information System (IRIS). *EPA/635/R-05/004*.
- Environmental Protection Agency (USEPA). 2002c. Child-Specific Exposure Factors Handbook. Office of Research and Development. *EPA/600/P-00/002B. September 2002*.
- Environmental Protection Agency (USEPA). 1998. Health Effects Test Guidelines OPPTS 870.6300 Developmental Neurotoxicity Study. Office of Prevention, Pesticides and Toxic Substances (7101) *EPA 712-C-98-239 August 1998*.  
[http://www.epa.gov/opptsfrs/publications/OPPTS\\_Harmonized/870\\_Health\\_Effects\\_Test\\_Guidelines/Series/870-6300.pdf](http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/870-6300.pdf)
- Hougaard, L.S., Lund, S.P., Haas, U. and Simonsen, L. 1999. Effects of prenatal exposure to toluene on postnatal development and behavior in rats. *Neurotoxicol. Teratol.* 21:241-250.
- Hsieh, G.C., Sharma, R.P., Parker, R.D. et al. 1990b. Subclinical effects of groundwater contaminants. III. Effects of repeated oral exposure to combinations of benzene and toluene on immunological responses in mice. *Arch. Toxicol.* 64: 320-328.
- National Toxicology Program (Huff, J.) 1990. Toxicology and carcinogenesis studies of toluene in F344/N rats and B6C3F1 mice. *NTP Technical Report Series No. 371. U.S.Dept. of Health and Human Services*.
- Ng, T.P., Foo, S.C., and Yoong, T. 1992a. Risk of spontaneous abortion in workers exposed to toluene. *Brit. J. of Ind. Med.* 49: 804-808.

Ono, A., Sekita, K., Ohno, K., Hirota, A., Ogawa, Y. et al. 1995. Reproductive and developmental toxicity of toluene. I. Teratogenicity study of inhalation exposure in pregnant rats. *J. Toxicol. Sci.* 20: 109-134.

Shields, H.C., Fleischer, D.M., and Weschler, C.J. 1996. Comparisons among VOCs Measured in Three Types of U.S. Commercial Buildings with Different Occupant Densities. *Indoor Air* 6: 2-17.

Slomianka, L., Rungby, J., Edelfors, S. et al. 1992. Late postnatal growth in the dentate area of the rat hippocampus compensates for volumetric changes caused by early postnatal toluene exposure. *Toxicology* 74: 203-208.

Slomianka, L., Edelfors, S., Ravn-Jensen, A., et al. 1990. The effect of low level toluene exposure on the developing hippocampal region of the rat: histological evidence and volumetric findings. *Toxicology* 62: 189-202.

Thiel, R. and Chahoud, I. 1997. Postnatal development and behavior of Wistar rats after prenatal toluene exposure. *Arch. Toxicol.* 71: 258-265.