Report of the Peer Consultation Meeting on Benzene

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

June 15 and 16, 2006
Erlanger, Kentucky

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

August 8, 2006

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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Executive Summary

A panel of scientists with expertise in toxicity, exposure, risk assessment, medicine, and children's health met on June 15 and 16, 2006, to conduct a peer consultation of a submission on benzene (CAS No. 71-43-2). 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 benzene to children, and if not, to identify data needs. The sponsors and authors of the benzene 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, the authors noted that the extensive data from animal studies are sufficient to address the hazard endpoints for all three tiers of the VCCEP pilot program. Benzene is absorbed by all routes. Its toxicity is caused by its metabolites, but benzene's mechanism of action is unknown for both cancer and non-cancer toxicity. Animal studies have shown benzene to be clastogenic and to induce leucopenia, lymphocytopenia, and solid tumors. It also is hematotoxic, immunotoxic and neurotoxic. Benzene does not impair reproductive performance in laboratory animals, but it causes developmental toxicity at doses that induce maternal stress. Transplacental effects occur for both hematopoietic and genetic endpoints. In humans, acute exposures produce central nervous system effects, while chronic exposures cause cytopenias, myelodysplasia, and acute myeloid leukemia (AML). In humans, lymphocytopenia appears to be the most sensitive non-cancer endpoint. The authors reviewed benzene's human reproductive and developmental toxicity data, stating that the available information is not sufficient to demonstrate that benzene causes adverse effects in these endpoints.

In discussing the hazard assessment, panelists noted that almost all of the animal toxicity and human effects data presented in the submission were from adults. They discussed the difficulty of relating these adult data to children, especially since benzene's mechanism of toxicity is unknown and no good animal model exists for AML. The panel discussed various approaches that might be considered, such as defining benzene's metabolism across age groups, exploring its site of action within the bone marrow, obtaining marrow tissue from children for *in vitro* testing, using PBPK (physiology-based pharmacokinetic) modeling, and identifying biomarkers relevant to toxicity. Some members questioned the adequacy of the immunotoxicity data presented. Panel members considered whether the hazard data addressed all of the target subpopulations, which range from the embryo and fetus, through the neonate, nursing infant, post-nursing child and adolescent, to the mature prospective parent. Panelists expressed divided opinions of whether the hazard data were sufficient for these subpopulations; however, the lack of animal studies on benzene-exposed nursing neonates and post-weanling animals was noted as a concern by almost all of the panelists. The panel was unable to determine the extent to which transplacental effects reported in animal studies are relevant for human risk assessment. Panelists said that the possible existence of a functional threshold for benzene's hematotoxic and leukemogenic effects is a key issue, but this issue could not be resolved without knowing the mechanism by which benzene causes its toxic effects, especially its clastogenicity.

The sponsor's presentation on the exposure assessment focused on the exposure pathways most relevant to children and to prospective parents. Exposure sources were divided into two groups: background and source-specific. Exposure scenarios from both source groups were presented, together with estimates of the typical and high-end exposures from these groups. Indoor air is the major source of environmental benzene exposure, while the highest exposures are from mainstream tobacco smoke and occupational sources. The authors said robust datasets exist for all major sources of benzene exposure, and no unique exposure scenarios exist, other than nursing infants ingesting breast milk from highly exposed mothers.

While acknowledging that the amount of data compiled and presented was impressive, several panel members raised questions about the high-end benzene concentrations estimated for both indoor and outdoor air. Some recommended a probabilistic exposure assessment to provide a more complete and explicit assessment of the distribution of exposure experienced by fetuses, children, and prospective parents. One member was concerned that the exposure concentrations estimated in the submission appeared too low given the benzene blood levels measured in human subjects in the NHANES III study. Other panelists also presented reasons why they were not convinced that the highest exposure values had been captured in the dataset presented in the submission. Some panel members believed the exposure database was sufficient and said all major sources of exposure had been identified and appropriately compiled in the submission's exposure assessment. The panel members voiced differing opinions on whether the birth to one-year age group should be divided into smaller intervals to differentiate neonates from toddlers.

The authors' risk characterization presentation summarized the hazard data in humans and animals, the exposures aggregated across all routes and sources, and the risk assessment approaches used for benzene's non-cancer and cancer endpoints. They said a key issue is the relative sensitivity of children compared to adults for AML. Because no direct data exist on children's leukemia risk from benzene, the submission used data on therapy-related AML to characterize benzene's leukemia risk across the infant to adult age groups. The authors compared the EPA's RfC/RfD values to three alternative values that used different choices of uncertainty factors. They also discussed risk assessment values resulting from the use of different cancer slope factors and non-linear dose-response models. The authors believed that the literature supports a functional threshold for cytopenias and for AML, and they recommended using a range of values for the benzene RfC/RfD.

The panel discussed various approaches that might be used to characterize benzene's non-cancer and cancer risk to children, including the approaches used by EPA and in the submission. Individual panelists stated and explained their own preferences for the most appropriate uncertainty factors (UFs) to use for benzene's non-cancer risk assessment. Although panel members suggested differing UF values, most of them said the approach and the UF values used by the EPA were highly conservative. Many, but not all, panelists expressed general agreement with the submission's risk characterization approach for benzene's non-cancer endpoints. The panel reviewed and compared the hazard quotient and margin of safety values listed in the submission and found them to be acceptable and sufficiently consistent. In discussing the cancer risk assessment, some panel members favored the approach used in the submission, while others questioned whether the literature truly supported a functional threshold for benzene's hematopoietic toxicity and AML risk. The panel also discussed how the risk characterization could be applied to the target subpopulations. Most panelists were more comfortable relating the risk characterization to prospective parents than to the embryo and fetus, the nursing infant, and the post-nursing child. The panelists differed in their opinions about the adequacy of the overall risk characterization. Some thought it was adequate, while others said a risk characterization of benzene could not be complete without more information on its mechanism of toxicity within all four of the target subpopulations.

In the data needs presentation, a sponsor representative noted that toxicity data were available for all of the Tier 1 studies and for most of the Tier 2 and 3 studies. In addition, there are extensive epidemiology and other human health data. He said the exposure data and assessment are adequate to evaluate exposures from all anticipated sources and emphasized that benzene exposures are declining. The sponsors did not identify any data needs for benzene.

The panel discussed a number of areas that could use further work and may be defined as data needs. The majority of panelists identified at least one data need in either exposure or hazard. A few panel members did not identify any data needs. The two most commonly identified data needs fell into two areas: obtaining a better understanding benzene's mechanism of toxicity and conducting a better

characterization of potential high-end exposures. Individual panel members offered specific suggestions for each of these areas. Other data needs mentioned by more than one panel member included the following: comparison of benzene's pharmacokinetics and toxicity across age groups; further investigation of the relationship between outdoor and indoor air concentrations; use of human biomonitoring data to estimate exposure; development of animal models for AML; and identification of relevant biomarkers for benzene's effects at low doses.

1. Participants

Sponsor

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

Presenters

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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

David Pyatt, Ph.D. Toxicology
Principal, Summit Toxicology, LLP

Ceinwen Schreiner, Ph.D. Developmental Genetics, ATS
Toxicology Consultant, C&C

Peer Consultation Panel Members[1]

John Christopher, Ph.D. Biological Science, DABT
Department of Toxic Substances Control, California EPA

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)

Jeffrey Fisher, Ph.D. Zoology/Toxicology
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[1] 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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Erica Liebelt, M.D. Pediatrics
University of Alabama at Birmingham

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Thomas McDonald, Ph.D. Environmental Health Sciences
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Ruthann Rudel, M.S. Hazardous Materials Management
Silent Spring Institute

Robert Snyder, Ph.D. Biochemistry
Rutgers, the State University of New Jersey

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

Observers and Other Attendees

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

2. Background

This peer consultation meeting has been 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 benzene assessment was submitted by the American Chemistry Council Benzene, Toluene, and Xylenes VCCEP Consortium (BP, Chevron Phillips Chemical Company LP, The Dow Chemical Company, E.I. du Pont de Nemours & Company, ExxonMobil Chemical Company, Equistar Chemicals, LP, Flint Hills Resources, LP, Marathon Petroleum LLC, Shell Chemical LP, Sterling Chemical Company, 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 better understand 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 should 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 benzene. Links to the submission document and appendices are available to the public on the Internet at http://www.tera.org/peer/VCCEP/Benzene/BenzeneWelcome.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 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 benzene submission consisted of 13 members independently selected by *TERA*. Each panel member disclosed information regarding potential conflicts of interest and biases for the VCCEP program in general, or for benzene and the Benzene, Toluene, and Xylenes VCCEP Consortium, or for any of the Consortium's member companies. *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, emergency and pediatric medicine, toxicology, and children's health. The panel received a copy of the submission and key references approximately six weeks 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. The sponsors also were given the opportunity to review the draft report to confirm the accuracy of their presentations and remarks. *TERA* staff resolved

any differences of opinion by reviewing materials from the meeting. This report is available on the Internet at http://www.tera.org/peer/VCCEP/Benzene/BenzeneWelcome.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. Several panel members noted additions to their disclosure statements. The panelists and *TERA* agreed that none of these additions were conflicts of interest according to the VCCEP policy, but they are listed here for completeness. Dr. Fisher added that he is doing work on jet fuel for the U.S. Air Force, and the fuel has benzene as a component. Dr. Hakkinen announced he will begin working as a Principal at Gradient Corporation on July 5, 2006. He had checked with Gradient and was told that no work on benzene relevant to this VCCEP submission had been done there. Dr. Kacew noted that he had joined the *TERA* Board of Trustees. Dr. MacIntosh added that he contributed to a US population based probability exposure model for benzene in the early 1990s.

One set of written public comments regarding the benzene submission was received (Appendix C).

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.

This meeting report is organized into four sections: hazard assessment, exposure assessment, risk characterization, and data needs.

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 benzene submission. These include BP, Chevron Phillips Chemical Company LP, The Dow Chemical Company, E.I. du Pont de Nemours & Company, ExxonMobil Chemical Company, Equistar Chemicals, LP, Flint Hills Resources, LP, Marathon Petroleum LLC ,Shell Chemical LP, Sterling Chemical Company, 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 benzene had been

selected for the VCCEP pilot program, and described benzene's chemistry and governmental regulations. See Appendix D for Mr. Jaques presentation slides, which provide further details.

5. Hazard Assessment

5.1 Sponsor Presentation on Animal Toxicology

Dr. Ceinwen Schreiner of C&C Consulting summarized the hazard data on animals contained in the sponsor's submitted assessment (see Appendix D for her presentation slides, which provide further details of her presentation). She noted that extensive toxicology data are available on benzene, and these data are sufficient to address the hazard endpoints in all three tiers of the VCCEP pilot program. She then reviewed the toxicity studies listed in each of the tiers and explained how the available laboratory animal information addressed the study endpoints, even though not every study listed in the tiers had been conducted. Benzene is absorbed by all routes, distributes throughout the body, and partitions into fat. Its toxicity is caused by metabolites rather than by the parent compound. Benzene metabolism occurs primarily in the liver, but also in the lung and bone marrow. Dr. Schreiner concluded that the animal studies showed benzene was essentially non-toxic acutely, although it was irritating to the eyes and skin. It was clastogenic and induced leucopenia, lymphocytopenia, and solid tumors in animals. Benzene is hematotoxic to animals and also causes immunotoxic and neurotoxic effects at doses similar to or higher than those causing hematotoxicity. Reproductive performance and fertility were not impaired. Developmental toxicity occurred, primarily at doses inducing maternal stress. Transplacental effects were demonstrated for both hematopoietic and genetic endpoints.

5.1.1 Clarifying Questions from the Panel

A panelist asked if any development effects in the fetus were noted at doses below those that produced maternal toxicity. The presenter answered that, in some studies, data on the dams were not reported; however, in those studies where data were reported, maternal effects indicative of stress, such as reduced body weight, were observed. Another panelist questioned the test methodology used in some of the genotoxicity studies, noting that volatile chemicals such as benzene are usually tested in closed systems in these assays. He also asked if the presenter considered benzene to be both mutagenic and clastogenic. Dr. Schreiner replied that the usual test methodology was employed in the genotoxicity assays, therefore closed systems were used in those tests where that is routinely done. She said the available data do not support the definitive conclusion that benzene is a mutagen, but it is clastogenic. One panel member questioned the presenter's statements that benzene produced no developmental effects but did produce fetal effects from transplacental exposure. He asked why these fetal effects were not considered to be developmental toxicity. Dr. Schreiner replied that the transplacental clastogenic fetal effects reported were noted at only one point in time. They were not followed throughout the development of the fetus, so there was no evidence that they persisted or were still present at birth. When asked by a panelist about her conclusion that no more animal testing was needed, the presenter clarified that, because of all the data on toxicity endpoints currently available, no more of the standard studies listed in the VCCEP tiers were needed.

5.2 Sponsor Presentation on Human Toxicology

Dr. David Pyatt of Summit Toxicology summarized the human hazard data in the submission (see Appendix D for his presentation slides, which provide further details of his presentation). He said that in humans benzene produced central nervous system (CNS) effects acutely, while chronic exposures affect the blood and bone marrow causing cytopenias, myelodysplasia, and acute myeloid leukemia (AML). Lymphocytopenia appears to be the most sensitive non-cancer endpoint. He discussed the different types

of leukemia, emphasizing that benzene produces only one type: AML. He noted that many other factors, such as cancer drugs, also can cause AML, and the great majority of AML cases have no readily identifiable cause. Dr. Pyatt said that although animal models exist for benzene's non-cancer hematopoietic toxicity, there currently is no good animal model for AML. He went on to explain benzene's metabolism, noting that metabolism is required for benzene toxicity. He presented the EPA's IRIS values for benzene's non-cancer and cancer effects and discussed the numerous studies that EPA used in selecting the IRIS values, as well as more recent studies. He reviewed the genotoxicity data, noting that the role genotoxicity plays in benzene's hematopoietic effects has not been established. He reviewed the human reproductive and developmental toxicity data, stating that the available information is insufficient to demonstrate that benzene causes adverse effects in these endpoints. Dr. Pyatt concluded by stating that benzene's mechanism of action is still unknown for both cancer and non-cancer toxicity. High-dose, chronic exposure to benzene has been positively associated with development of AML; however, studies investigating the potential association of parental benzene exposures and development of childhood leukemia have been equivocal.

5.2.1 Clarifying Questions from the Panel

One panelist asked if the 2005 Knox epidemiology study on children and cancer (Knox, 2005) had been reviewed. The presenter said it had, but the report was on all types of children's cancers caused by industrial emissions in Great Britain, not specifically on AML or on benzene, so its usefulness was limited. Another panel member noted that cases of childhood myelodysplasia often progressed to AML, so reports on this disease should be closely monitored. Asked if benzene was metabolized in the placenta, the presenter said this was not known. One panelist noted that a study by Lindstrom et al (1994) on benzene exposure from showering reported that 60% of systemic exposure was via the dermal route and only 40% via inhalation; therefore, the dermal exposure route for benzene may be high in some situations and should not be ignored.

5.3 Panel Discussion of the Hazard Assessment

The panel discussion of the hazard assessment addressed these four charge items, which are summarized in the four 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. *Are the human and animal hazard data sufficient to determine if the transplacental effects on hematopoiesis and genotoxicity reported in animals are relevant to human risk assessment? If not, what additional data might resolve this issue?*

4. *Is the presence of a functional threshold for benzene-induced hematotoxic and leukemogenic effects adequately supported by the literature?*

5.3.1 Information to Identify and Assess Hazards

Given that almost all of the animal and human data presented were from adults, a panelist wondered how best to bridge the effects reported in adults to those likely to occur in children. He thought determining

benzene's mode of action and more precisely defining its ADME were both highly important. He suggested key areas to explore included the place in the myeloid cell line of development where the benzene effect occurs, the cellular or intracellular location within the bone marrow where benzene is metabolized, and the identities and concentrations of the benzene metabolites at this location. Another panel member added that not enough is known about the lower end of benzene's dose-response curve because we do not have the proper animal models. He said the Tg.AC mouse model might be the best animal model to use because it is the only model to date in which benzene induces a granulocytic leukemia, which is the type observed in humans. The fact that it does so in 6 months is an added advantage. Looking at the way biomarkers relate to benzene toxicity also seems like a good way to proceed, but we first need to identify the correct biomarkers for humans. Several panel members thought that obtaining marrow tissue from children would be a great help in pursuing this work. They agreed that obtaining children's marrow tissue would be difficult, but some thought such tissue might be available occasionally from children being treated for hematopoietic or other diseases. One member thought that, in the absence of having children's tissues available, some useful information could be obtained by examining the known differences between adults and children for parameters such as enzyme activities, organ blood flows, breathing rates, ADME, and so forth.

The panel discussed how PBPK modeling might help relate adult data to children. One panelist explained that although several good models existed that supplied ADME information applicable to benzene, none of the models provided information on events occurring within the bone marrow, which is the information really needed. Dr. Pyatt said that he thought the PBPK model of Cox (Cox, 2000) did address bone marrow. Another author of the benzene submission, Mr. Sean Hays, noted that benzene must be metabolized for toxicity to occur in children, as is the case in human adults and in animals. Children do not have the CYP2E1 enzyme to metabolize benzene at birth, but this enzyme develops by one year of age. Mr. Hays indicated that to the degree that children less than one year of age have a reduced capacity to metabolize benzene, they should be protected from benzene toxicity. In mouse studies, benzene administered to dams was transferred across the placenta to the fetuses. The fetuses could not metabolize it and, therefore, they were protected from toxicity. In response to questions from the panel, the presenters responded that it was not known if CYP2E1 levels continue to increase in children after the age of one year. It also was not known if benzene metabolism needed to occur in the bone marrow to result in toxicity. CYP2E1 activity is expressed primarily in the liver, not in the bone marrow. One panel member said that it made no sense to him that benzene metabolites formed in the mouse dams would not cross the placenta into the fetus. The presenters responded that no benzene metabolites were detected in the mouse fetal tissues, using the same degree of sensitivity that detected metabolites in the dams. The study investigators reported a general trend of firmly tissue-bound metabolites in the maternal liver and kidney. Another panelist said that experiments conducted in his laboratory (Keller and Snyder, 2001) had demonstrated that demonstrated that administration of benzene to 2-day-old mice resulted in the full range of benzene metabolites in urine and evidence for the production of reactive metabolites. He said the investigation did not study metabolism directly in embryos or fetuses; however, he believed metabolic activity existed in the fetus because activity was seen in neonates 2 days after birth. The panelist added that results suggest that the mouse and rat differ in this regard, but it is not known if the human is more like the mouse or the rat. He noted that his experiments in mice also found that benzene and its metabolites can be transferred to the neonate via the mother's milk.

Two panelists questioned the adequacy of the data available on immune system effects. One member said benzene has been known to cause death in humans by destroying their immune systems.

One panel member suggested the tiered process used in the VCCEP pilot program might not be the best approach to answer questions related to children. The tiers indicate what data are available but not how to relate the data to children. Other panelists added that if benzene's mechanism of action were known the standard long-term studies listed in the tiers would be unnecessary to characterize benzene's risk to

children. They said the lack of a 2-generation study on benzene was a data gap, but not a data need. Other panelists mentioned that everyone has background levels in their tissues of chemicals that are benzene metabolites (e.g., phenol, hydroquinone), but that have originated from non-benzene sources. It is not known if these chemicals are the ones responsible for benzene's leukemogenic activity, or if these chemicals from non-benzene sources are responsible for the background levels of leukemia existing in the human population.

5.3.2 Hazard Data on Subpopulations

A panelist said the sponsors' document adequately summarized the epidemiology studies on prospective parents and correctly identified the many confounding factors existing in these studies. While some studies were positive and some negative, no association was apparent overall between benzene exposures and increased incidences of cancer. There also was no apparent effect of increased cancers in embryos or fetuses exposed *in utero* via maternal exposures to benzene. The panelist concluded that sufficient data existed on the two target populations noted above (the prospective parents and the embryos and fetuses) to support a lack of effect for benzene in these populations. Another panel member disagreed, saying that the database on these two populations was not adequate. A third panelist thought the weight of evidence was predominantly negative and indicated no benzene effect, but he would have liked to see more studies comparing different age groups. He wondered whether NADPH-dependent quinone oxidoreductase (NQO1) might be involved in benzene's hematopoietic toxicity because he thought this enzyme was age dependent, but he stressed that all enzymes should be considered together, not singly, because the ratio of the different enzymes is important.

For the target population of nursing infants, a panelist concluded that benzene toxicity was unlikely to be a problem for them in the U.S., but he said the situation might be different in others countries where infants ingest benzene via the milk of nursing mothers exposed to benzene in their occupations. Little information was found regarding post-nursing children through adolescence to the age of sexual maturation. The panelist said that unfortunately not many animal studies on benzene-exposed nursing neonates or post-weanling animals were available to supplement the few human studies. When asked if any studies existed on post-natal animals dosed directly with benzene, the presenters said only a few of these types of studies existed, and they are controversial.

In response to a panelist suggestion to mine the data contained in cancer registries to find incidences of childhood AML, Dr. Pyatt responded that this had been done. The cancer registries provided data indicating that children who had been treated with cancer drugs showed no increased risk of AML compared to adults. Dr. Pyatt acknowledged the point made by panel members that AML resulting from benzene exposure may occur by a different mechanism than AML caused by cancer drugs ("therapy-related AML"), but he said it also was possible that the same mechanism may be involved. Responding to a panelist's comment that AML is seen more frequently in older children, Dr. Pyatt said his review of the literature failed to show any age dependence for AML from therapy-related agents. He encouraged the panel to consider the similarities in the cytogenetics and morphological characteristics of therapy-related and benzene related AML as evidence that the mechanisms could be similar. He also noted that the findings of no age-dependent changes in tAML risks for the two classes of drugs which act via different mechanisms of action suggests that the childrens' developing hematopoetic system may be no more sensitive to any chemical leukemogens.

5.3.3 Hazard Data to Assess Transplacental Effects

A panelist stated that the existing dataset on benzene toxicology is not able to answer the degree to which transplacental effects reported in animals are relevant to post-natal animals or to human risk assessment.

The few studies are from laboratories whose results have not always been reproducible by others. More work is needed to explain the results reported from transplacental studies conducted on hematopoiesis and on cancer. The use of cytogenetic biomarkers might help, but the right biomarkers have yet to be identified. Some panelists asked for additional information about the studies of Keller and Snyder (1986, 1988), which reported changes in hematopoietic cells after exposing mice to benzene *in utero.* They wanted to know if the findings from these studies could be applied more generally and used in studies with older animals. The presenters called on Dr. Willem Faber, a consultant to Lyondell/Equistar Chemical Company who was present in the audience, to comment on these studies. Dr. Faber said different mechanisms are operating in embryo and fetal hematopoietic systems than in post-natal animals or in adults. As a result, he suggested that the methods used in the studies of Keller and Snyder (2001) were not appropriate to use in post-natal, young, or adult animals. He stressed that assays intended and validated for one life-stage should not be used in other life stages without proper validation. One of the panelists replied that Dr. Faber's objections were not warranted unless he could show data to refute the Keller and Snyder (2001) study conclusions.

5.3.4 Support for a Functional Threshold

A panelist said the question of whether a functional threshold exists for benzene-induced hematotoxic and/or leukemogenic effects is a key issue. He disagreed with the submission's conclusion that the available epidemiological data strongly support a threshold for benzene's hematopoietic toxicity and thinks that the data are mixed; for example, he noted that the large Chinese study of Hayes et al (1997) does not support a threshold. He noted the EPA has issued guidance for how to address whether thresholds exist, and the agency has set the bar quite high to support concluding that there is a threshold. The panelist emphasized that one important parameter to consider is whether benzene exhibits genotoxicity, and it does. He thought, and other panelists agreed, that knowing benzene's mechanism of action, especially its mechanism of action in causing clastogenicity, was necessary to explore further the threshold question. Dr. Pyatt responded that if the mechanism of benzene's clastogenicity involves changing spindle formation of the chromosome, then there would be a threshold. The panelist said he would agree if this were known to be the mechanism. Another panelist noted that the bar for establishing a threshold should be set at the highest level for benzene because the chemical is positive in humans. Another panelist added that some of benzene's toxic effects likely have thresholds and others likely do not. He said the question of a threshold should be asked separately for each key toxicity endpoint, including those related to hematopoiesis, cancer, and the immune system.

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 D for her presentation slides, which include further details). She noted this assessment focused on those exposure pathways most relevant to children and to prospective parents and divided the exposures into two groups: background and source-specific. Exposure values were presented as "typical" (average or mean) or as "high-end" (90^{th} or 95^{th} percentiles). Six target groups were considered in the exposure assessment: five age ranges of children and prospective parents. Ms. Panko reviewed each of the background sources and also the source-specific exposures, providing both typical and high-end concentrations. She talked in some detail about reports of benzene in soft drinks because this exposure source has received considerable publicity recently, even though its contribution to total human benzene exposure is minimal. Ms. Panko presented a series of bar graphs comparing the contributions of the various benzene sources to typical and high-end chronic exposures with the values

expressed as annual average daily doses. Indoor air is the major source of environmental benzene exposure, while considerably higher exposures may result from mainstream tobacco smoke and occupational sources. Ms. Panko concluded that robust data sets exist for all major sources of benzene exposure to the six target populations considered in the assessment and that no unique exposure scenarios existed for these target populations, other than nursing infants ingesting breast milk from highly exposed mothers.

6.1.1 Clarifying Questions from the Panel

In response to questions from the panel, Ms. Panko stated that the benzene exposure information obtained for Harris County, Texas, did not include health effects and that benzene concentrations in outdoor air showed seasonal variation, tending to be lower in the summer months. Another panelist said he had reviewed the Harris County air data from the EPA website (http://www.epa.gov/ttn/airs/airsaqs/detaildata/downloadaqsdata.htm) but could not find the benzene concentrations presented in the submission. He asked why the concentrations listed in the sponsors' submission were only 53% of the values on the EPA website. Ms. Panko responded that the EPA data were reported in units of parts per billion carbon. These values were divided by 6 and then multiplied by 3.19 to convert them to a benzene concentration in ug/m^3. The panelist thanked Ms. Panko for this explanation and then noted that Table 7.5 (page 104) shows 2003 annual mean benzene concentrations for each of two monitors in Harris County. One of the concentrations is 8.4, which is nearly double the average of 4.4 in 2003 for the county as reported in Table 7.6b (page 105). He added that, if one looks at other years, many locations have higher concentrations of benzene than Baytown. Ms. Panko replied that the authors of the submission focused on the most recent data because of the downward trend in ambient air benzene concentrations. She said the downward trend is evidenced by EPA's trends analysis, which showed a 47% decrease in ambient benzene concentrations from 1994 – 2000 (Figure 5.2 on page 32 of the benzene submission.), and therefore the historical data would not be representative of current ambient air levels or predictive of future concentrations. Ms. Panko added that the authors' analysis was based on the 2003 TRI ranking of top facilities reporting air releases of benzene, which was the most current information available prior to submission of the benzene VCCEP document. Consequently, the authors used the ambient air measurements from that same year.

One panel member asked why the children from birth to one year of age had been combined into a single exposure group. She said the neonates and toddlers included in this group vary considerably in their food and water consumption, activities, and in metabolic parameters such as breathing rates. Ms. Panko acknowledged this was true, but she pointed out that the children within this group experienced similar benzene exposures, both from the air and from source-specific exposures. In addition, the children's age grouping used in the benzene submission conformed to the age grouping used in the EPA's cancer guidance document.

One panel member posed several specific questions related to the exposure data presented from Harris County, Texas. These questions included how the actual values were determined, how the data from different county monitoring stations was compiled and evaluated, how mobile sources of benzene (vehicles) were included, and how it could be assured that the highest exposure concentrations were used in the high-dose values presented in the submission. The presenter responded that the answers to these questions were not immediately available, but they were included in the source documents. The panelist suggested that the source documents be reviewed and the answers included in the benzene submission.

Other members questioned how "occupational" was defined in the submission. They also asked whether the exposure assessment had included the contributions of burning incense and new car interiors, and whether the benzene exposure of premature infants had been considered. The presenter replied that their presentation of occupational exposures was intended to include any type of job: not only industrial

activities, but also toll booth workers and police directing traffic. She added that benzene from burning incense or from new car interiors had not been evaluated. A separate exposure grouping for premature infants to benzene was not considered.

Asked whether the submission considered that a given *exposure* to benzene was not the same as a given *dose* of benzene, the presenter explained that this difference was accounted for in the submission by using a 50% absorption factor for benzene after inhalation exposure, as is done by the EPA.

Noting that we are all exposed to benzene on a continuum, a panelist asked if the mean exposure level was really the 50^{th} percentile, if the 95^{th} percentile was really the high-end, and how this varied regionally within the country. The presenter responded that within the lower 48 states the benzene indoor air concentration ranges from 1.5 to 4.0 ug/m^3 with the typical value being 2.5 ug/m^3. The high end indoor air was calculated as the average of the indoor air samples from the Adgate attached garage home study (Adgate et al. 2004). This is conservative because home with attached garages are known to have higher indoor benzene concentrations, and most people living in the lower 48 states do not live in homes with attached garages. Many live in homes with separate or no garages, or in apartments or multi-family units. Also on the subject of indoor air, another panelist asked for clarification of the studies done on indoor air in schools. Referring to pages 118-120 of the submission, the presenter said many assessments of school air are conducted each year for individual schools in response to site-specific concerns raised by parents and others. These assessments routinely measure total VOCs (volatile organic compounds) rather than benzene specifically, and few of the studies are ever published. Those studies that are published are not necessarily representative of in-school air quality regionally or nationwide.

6.2 Public Comments on the Exposure Assessment

Prior to the meeting, a set of written public comments regarding the exposure assessment had been submitted to *TERA* from scientists at the EPA. These comments were forwarded to the panel members and to the benzene sponsors and presenters. All parties were instructed to consider the public comments in their meeting presentations and subsequent discussions of the exposure assessment. (A copy of the written public comments is located in Appendix C.)

Ms. Patterson of *TERA* provided a brief oral summary of the written comments for the panel and other meeting attendees, and the Chair asked whether anyone wished to respond to them. Mr. Jaques said he disagreed with the statement in the written comments that water can be a significant sink for benzene. He said the Level III fugacity modeling results from EPA assumed equal emission rates to all media, which is not supported by the available TRI data that indicate that almost all emissions are to the air.

6.3 Panel Discussion of the Exposure Assessment

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

5. Are the potential sources of benzene 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 have been calculated appropriately and correctly.

6.3.1 Sources of Exposure

A panelist stated that the major sources of benzene appear to have been identified, although more information could have been provided for consumer products. The process used by the authors to identify the sources should have been more fully described in the submission so that the panel and others could evaluate the adequacy of the process to identify all of the benzene sources. Other panelists noted additional benzene sources that they thought should have been considered, including the burning of incense, the interiors of new cars, and small engines.

6.3.2 Adequacy of Exposure Data

Several panel members commented that the submission did a good job in addressing all of the various aspects of exposure: sources, routes, frequency, duration, and intensity. Other members expressed some reservations about whether the information presented was adequate. One panelist acknowledged the amount of data compiled and presented was impressive, but she was unsure how representative the data were. She said that the potential benzene exposures to neonates and to infants born prematurely were of unknown importance. Another member noted that the term "dose rate" had been mentioned, and he asked whether the submission should have provided more explanation of this term so the panel could determine if it were an issue. Another member responded that the dose rate was certainly important, but dose rate data are not available for patients on an individual basis. Sometimes the benzene blood levels or urine phenol levels are measured in patients, but these measurements occur at varying times after the exposure event and provide little information about the dose rate that has been experienced. One member said the exposure assessment was not adequate for mobile source exposures. He added that the panel did not know if the values presented from the counties with the highest emissions (see Tables 7.4 and 7.5 on pages 103-104 of the submission) were truly the highest exposure levels in the database.

6.3.3 Application of Exposure Data to Children

Noting that charge question 7 uses the term "appropriate," a panelist said criteria to judge "appropriateness" are needed in order to discuss the issue, and he offered his thoughts on criteria that could be used. One criterion could be internal consistency. The exposure data are not internally consistent if one back-calculates from the NHANES III benzene blood level data reported by Ashley et al. (1994) to estimate the exposures required to produce these blood levels. When this is done, the exposure estimates provided in the submission appear to be too low. A second criterion could be external consistency: whether the data presented are consistent with what is expected for concentrations of benzene in outdoor and indoor air if benzene acts like other VOCs. On this point, the panelist disagreed with how the submission treated outdoor and indoor air differently. The panelist went on to say the exposure data presented probably were reliable and reproducible, but he was not sure the data were representative. He also was unsure the highest exposure scenarios had been captured. He mentioned an example scenario of the indoor air of a house with an attached garage, located near a point emission

source in a county with generally high outside air benzene levels. Other panel members were less critical of the submission's exposure assessment. One member was concerned that using high-end values for multiple parameters would unduly multiply conservatism. Another said the submission clearly explained what was done, and she was satisfied with the way the exposure data were presented. Several members recommended using a stochastic model to assess and present the exposure data. They said that using a stochastic or probabilistic approach would give added confidence to the conclusions.

On the subject of age groupings, the panel discussed whether the birth to one-year age group should be divided into smaller intervals to differentiate neonates from toddlers. Some members were not certain that having smaller intervals within this group would be useful. A panelist explained that the hazard assessment does not have the data or tools to calculate reference doses for such small age ranges. Another panelist suggested one could take the standard reference dose and apply an additional uncertainty factor (UF) for any subgroup that might be shown to be more susceptible to benzene toxicity, but the first panelist reminded the panel that the standard lifetime reference dose should already have all the most susceptible subgroups covered. When yet another panelist noted that the epidemiology data failed to show that children of any age were more susceptible than adults, another responded that the concern was not with children showing increased effects, but rather that exposures occurring during certain childhood periods might result in more toxic effects developing later in life. Also on the subject of age groups, several panelists thought that some scenarios did not include all relevant age groupings. They recommended that Table 7.2 on page 99, together with the related text in the submission, be revised to subdivide the 6 to <16 year old age group and include exposures from mainstream tobacco smoke, refueling vehicles, small engine use, and occupational activities for older children under 16 years of age.

6.3.4 Exposure Data for Target Subpopulations

A panelist said it was not possible to say with certainty whether the exposure data are sufficient to assess the subpopulations, because of the inconsistency between the benzene blood level data from the NHANES III study (Ashley et al. 1994) and the estimated exposure values presented in the submission's exposure assessment. This inconsistency suggests that some additional exposure might be occurring which was missed in the submission. Another panel member was not concerned by the inconsistency. He said the blood values obtained from the NHANES III study were from a composite of single samplings of each participant. Many unknown factors could have influenced the individual point values; for example, someone may have been exposed to cigarette smoke immediately before their blood was drawn and some might metabolize benzene differently. The panel Chair asked Ms. Panko what degree of uncertainty existed in the exposure values presented in the assessment (pages 152-154). She replied the numbers had a low degree of uncertainty and were representative of the general population with the mean exposure values having less uncertainty than the high-end values. She said there was no inconsistency in finding blood values that were eight times greater than expected from estimated exposures because of the variation in the population and in back-calculating using the PBPK model. The chair asked Mr. Hays to further address these uncertainties inherent in the PBPK model. Mr. Hays explained that the PBPK model assumes steady state conditions, but these conditions do not really exist. The approach does not capture pharmacokinetic variability. Temporal and concentration variability also are factors. Some of the panelists were convinced by this impromptu presentation, while others continued to have concerns about inconsistency.

One member of the panel noted that exposures to mothers staying home with children were not presented, and the amount of benzene transferred across the placenta to embryos and fetuses was not really known. She added that with the United States population of about 300 million using the 95th percentile as the high-end exposure leaves many people with exposures higher than this value. Another panelist responded that using percentiles higher than the 95th percentile often was not feasible because doing so would result

in values that were less reliable and highly variable. She said it was not possible to estimate accurately the very highest benzene levels to which an individual might be exposed.

6.3.5 Exposure Calculations

TERA staff spot-checked several of the submission's calculation prior to the meeting. A few errors were found and relayed to the sponsors. An errata sheet correcting these calculation errors and additional mistakes identified by the sponsors was prepared and distributed to the meeting attendees. The errata sheet can be found on *TERA's* benzene web page http://www.tera.org/peer/VCCEP/Benzene/BenzeneWelcome.html.

7. Risk Characterization

7.1 Sponsor Presentation

Mr. Sean Hays of Summit Toxicology summarized the risk characterization data presented in the sponsor's submitted assessment (see Appendix D for his presentation slides, which include further details). He provided overviews of the hazard data in humans and animals, of the exposures aggregated across all routes and sources, of the risk assessment approaches used for non-cancer and cancer endpoints, and of the children's relative sensitivities and dose-response data. He said the key issue was the relative sensitivity of children compared to adults for cytopenias and for AML. He stressed that because no direct data exist on the risk of leukemia in children following exposure to benzene, data on the occurrence of therapy-related AML and acute non-lymphocytic leukemia (t-AML/t-ANLL) were used to characterize the effects of age on chemically induced leukemia risk. Dr. Pyatt presented an analysis on the effects of age on chemically induced leukemia risks using the clinical literature on the occurrence of therapy-related AML and acute non-lymphocytic leukemia (t-AML/t-ANLL). After Dr. Pyatt presented data to support a conclusion of no need for additional child-specific safety factors for chemically-induced cytopenias or AML, Mr. Hays presented the EPA's RfC/RfD values listed on IRIS and compared these values to three alternative RfC/RfD values based upon selection of different uncertainty factors. He discussed cancer slope factors and non-linear dose-response models and presented risk assessment results according to age and exposure source. He concluded that the scientific literature supports a functional threshold for cytopenias and for AML and also the use of a range of values for the RfC/RfD is preferable to using single values.

7.1.1 Clarifying Questions from the Panel

One panelist thought the mechanism by which alkylating agents caused cancer was well known and he asked why the sponsors thought benzene could act in the same way, given its chemical structure. Dr. Pyatt responded that it does not appear that benzene's mechanism of action is precisely the same as alkylating agents. He added that the similarities in the cytogenetics and morphological characteristics of therapy related and benzene related AML cases suggest a similar pathogenesis. Dr. Pyatt also indicated that the analysis of the therapy-related AML literature suggested no changes in age-dependent risks of secondary AML (between children and adults) following two different types of chemical treatments (with different mechanisms of action), suggesting that the age-dependent effects of AML may be irrespective of the chemical or mechanism of action. He added that from what is known about benzene, the mechanism appears to be the same as with alkylating agents. Other members asked about the decline in environmental benzene concentrations that were not reflected in declines in AML cases. They wondered if any statistical evaluations had been conducted to confirm that any decreases in AML over the given

time period could be detected (the answer was no), and they said that the total number of AML cases might have stayed level because AML is caused by many things besides benzene.

7.2 Panel Discussion of Risk Characterization

The panel discussion on Risk Characterization addressed three charge items:

10. Discuss whether the risk characterization methodologies employing a Margin of Safety (MOS), Hazard Quotient (HQ), and cancer risk approaches are appropriate for benzene.

10 a. The authors calculate the non-cancer risk with a HQ approach using EPA's IRIS RfD (labeled "high") and an alternative RfD calculated by the authors (Alternative #3, labeled "low"). To characterize risk further for non-cancer effects, the authors also calculate a MOS based on a Point of Departure (POD) value derived by the European Union (Rothman NOAEC of 1 ppm; from ECB, 2003). Do you agree with these approaches? Were the appropriate values (i.e., for RfD and POD) used?

10 b. The authors presented the cancer risk associated with benzene exposure in two ways. They estimated excess lifetime cancer risk based on a range of cancer slope factors. They also calculated cancer risk using a MOS approach based on a non-linear dose response relationship for the induction of AML (acute myelogenous leukemia). For this latter approach, they used a Critical Exposure Level (CEL) derived by the European Union (ECB, 2003) of 0.1 ppm (includes a MOS of 10). What approach do you think is most appropriate to use? Do you agree with the Cancer Slope Factors and POD used for the MOSs?

11. Discuss whether the risk characterization is sufficient 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.

12. In evaluating the potential for age-related differences, the report discusses whether children are more sensitive to benzene-induced hematopoietic toxicity or AML than are adults (sections 8.2.1 through 8.2.1.3, pp. 160-163). This analysis is based on literature describing children's treatment with chemotherapeutic agents. Does this analysis sufficiently support the conclusion of no age-related differences in sensitivity to benzene?

7.2.1 Non-cancer and Cancer Risk Characterizations

Non-cancer

The submission's discussion of non-cancer risk assessment presented the EPA RfD/RfC approach as listed in IRIS and also three alternatives to the IRIS value. A panel member briefly reviewed the EPA RfD/RfC approach, explaining the uncertainty factors used to derive reference values. The panel member noted that EPA used a standard deviation of 1 for the decrease in absolute lymphocyte count as the most sensitive endpoint in its benchmark dose (BMD) approach. The panelist stated that such a decrease is not necessarily an adverse effect and using this default decrease in lymphocytes should have been checked against standard clinical judgments. Furthermore, he questioned the EPA's and the submission's use of a 3-fold uncertainty factor with a lower bound confidence limit on the benchmark dose (BMDL), because this is not consistent with the current EPA practice. He disagreed that an uncertainty factor of 3 was needed for the subchronic-to-chronic UF for this VCCEP analysis, (although he thought this was appropriate for the IRIS assessment), because the childhood exposure of concern for VCCEP is much less than the lifetime exposure for the RfD. In addition, the critical effect is not in a young population. He

thought the sponsors' submission was correct in assigning a value of 1 for the subchronic-to-chronic UF (which was done for Alternatives 2 and 3 in Table 8.1 on page 174 of the submission). The panelist noted that the submission's use of a UF of 3 rather than 10 for interspecies variability in all three of their alternatives was plausible, because the authors state that children appear resistant to AML resulting from therapy-related drugs, and they believe therapy-related AML can serve as a surrogate for benzene-caused AML. However, the panelist believed this rationale needed additional justification for the non-cancer critical effect of decreased lymphocytes. This panelist also maintained that a database uncertainty factor of 3 was reasonable, based on the lack of direct data from young animal testing. In summary, the panel member said that Alternative 2 (Table 8.1 on page 174 with explanatory text on pages 164-166) seemed the most appropriate for deriving a benzene non-cancer RfC/RfD, although his uncertainty factor choices were somewhat different from those of the authors.

Regarding the point of departure (POD) for the MOS, the panelist said the submission should have provided the scientific rationale for using the European Union POD value (1 ug/m^3). In addition, he said providing a range of PODs would have been preferred.

Another member stated he would be willing to use the EPA's IRIS values, although he thought they were conservative. He agreed with the rationale the sponsors' submission used to present the three alternatives to the IRIS derivation. This member presented his own preferences for UFs to derive a benzene non-cancer RfC/RfD. His values resulted in a composite UF of 30 (LOAEL-to-NOAEL extrapolation UF_L = 1; intraspecies variability UF_H = 10; subchronic-to-chronic UF_S = 1; database deficiency UF_D = 3).

In response to questions from the panel, Mr. Hays stated that the RfC and RfD values from the three alternatives assumed continuous benzene exposure over a 70-year human life span. He also noted that, at least in mice, peak benzene concentration rather than AUC (area under the curve) was a better predictor of toxic response.

To evaluate consistency in the risk assessment conclusions, the panel reviewed the bottom-line non-cancer hazard quotient values in Table 8.4 (pages 177-178) and found the highest values to be approximately 1. They also reviewed the bottom-line non-cancer MOS values in Tables 8.9 and 8.10 (pages 186-189) and found the lowest values to be approximately 100. Panel members concluded that the comparison of these two parameters (HQ and MOS) was within an order of magnitude, and therefore the parameters were roughly consistent.

Cancer

A panelist said he appreciated the manner in which the submission presented a full range of approaches to consider for the cancer risk assessment. He said EPA likely chose to use a default linear approach for calculating hazard quotients and excess cancer risks because of the uncertainty that exists regarding a possible threshold for benzene's effects; however, he prefers the approach presented in the sponsors' submission (summarized on pages 192-194). He said the rationale in the submission is both thoughtful and reasonable, and it also is consistent with benzene's known biological activity. He did have two concerns with the submission's arguments used to support a threshold for benzene's hematopoietic toxicity and AML risk. One concern was that medical literature on the effects of radiation exposure from atomic explosions showed that people who were exposed when young had higher incidences of leukemia than those who were exposed when older. The second concern was that the studies of Maltoni et al. (1983 and 1989) indicated that a 20% increase in exposure time during early life resulted in a doubling of tumor incidence. The panelist suggested that the authors of the submission consider how these two issues might affect the rationale presented for a benzene toxicity threshold. In addition, the panelist said that although the "high" and "low" guidance values presented in the submission were acceptable and likely captured the entire range of cancer risk estimates, he would have preferred that the submission present a "central" guidance value also. Other panel members noted that Table 8.6 (page 182 of the submission)

shows a difference of about 300 times between the highest (8E-05) and the lowest (3E-07) estimates for Urban - High End cancer risk values. Several panelists said this span was large enough to include the range of reasonable cancer risk estimates.

One panelist said that his review of the benzene exposure estimates in the submission led him to conclude that reasonable high-end exposures could be two to three times higher than the high-end values presented. He asked what effect such higher exposures would have on the cancer risk estimates (Table 8.6). Another panel member replied that if the exposures were truly two to three times higher than presented, the cancer risk estimates would be increased by only about 30%. The presenters noted that, even if the panelist was correct that exposures might be higher than the values presented, only the high-end estimates (Table 8.6) would be increased, not the typical values. Another panelist added that it is not uncommon for high-end exposure estimates like those presented in the submission to vary by a factor of two or three.

7.2.2 Applying the Risk Characterization to Target Subpopulations

Addressing the question of whether the risk characterization of benzene was sufficient for all target subpopulations, a panel member stated that the risk to any of the subpopulations cannot be fully characterized without knowing benzene's mechanism of toxicity. She said the increasing ability to detect benzene at low levels is increasing public awareness and concern; therefore, scientists need to better communicate with the public to help them understand the difference between perceived risk and actual risk. Regarding the four subpopulations listed in the charge item, the panelist said that in her opinion the available data are sufficient for a risk characterization on prospective parents. She thought more data were needed for sufficient risk characterization of the other three subpopulations (embryos and fetuses, nursing infants, and post-nursing children) because of uncertainties about latency and the activities of key enzymes such as CYP2E1. In addition, she noted that both the hazard and exposure data are limited in children, and no studies of high-level exposures in children are available. Another panelist disagreed that more data are needed on embryos and fetuses. He said that the data currently available from animal and epidemiology studies, together with the available information on key enzymes, are sufficient.

One panelist referred to the non-cancer hazard quotients and the cancer risk estimates used for benzene's non-cancer and cancer risk characterization (Table 8.4, pages 177-178; and Table 8.6, page 182). Regarding Table 8.4, he said that even if the hazard quotients were increased 30% (assuming the possibility of higher-than-presented exposures as suggested by a panelist in the paragraphs above), the numbers in this table would then need to be reduced by 3-fold because the uncertainty factor of three-fold used in the development of the RfD/RfC for subchronic to chronic extrapolation is not needed in the case of children, since they do not remain children for an entire lifetime of exposure. The net results would be that Table 8.4 would have similar or lower hazard quotient numbers than those presented, and the highest hazard quotient would be less than 1. Regarding Table 8.6, he said that the cancer risk estimates listed were overly conservative by a factor of about 2-fold because the estimates assume that benzene exposure continues throughout life up to 70 years of age, but the populations of concern for VCCEP are not individuals at 70 years of age. None of the other panelists voiced disagreement with this reasoning, but one member said it was important to realize that benzene does two things at the same time: it depresses the bone marrow to cause cytopenias, and it stimulates cell growth to cause AML. In other words, benzene initiates tumors, and then kills some of them. He hypothesized that if benzene exposure occurs at a young age and then stops, the result over a lifetime may be the same or more tumors than if the benzene exposure continued throughout life.

7.2.3 Age-related Toxicity Differences

A panelist explained that although the mechanism of benzene toxicity is not known, it is unlikely to be via DNA adduct formation. Therefore, benzene's mechanism is probably not the same as the mechanism of

alkylating agents, but this may not make any difference. He noted that it also is not known whether benzene's mechanism of toxicity is the same in children and adults. If the mechanism in children and adults is the same, then the sensitivity of children is likely to be the same as in adults. Because of this reasoning, the panelist said he agreed with the sponsors' submission lowering the intraspecies UF from 10 to 3 for children for the non-cancer assessment. Another panelist said this logic would also apply to the cancer risk assessment, but, if there are doubts, the EPA's UF for genotoxic cancer in children can be added: 10-fold for children's exposure during years 1 through 3, 3-fold for years 4 through 15, and 1-fold for the remaining time of exposures of interest. He said that combining these values for the different age groups results in a UF of about 1.6-fold overall.

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 hazard, he noted that benzene toxicity data are available for all of the Tier 1 studies (see Appendix D for his single presentation slide). Toxicity data also are available for most of the Tier 2 and 3 studies. In addition, extensive epidemiology and other human health data are presented in the submission. He acknowledged an animal 2-generation reproduction toxicity study has not been conducted on benzene, but he described several existing studies that evaluated benzene's effects on fertility and reproductive performance. He stressed that while some additional toxicity information might be gained from a 2-generation study, the value of conducting such a study at this time would be quite limited. He noted that when the Organization for Economic Co-operation and Development (OECD) reviewed benzene in October 2005, it concluded that no further testing was warranted on benzene's reproductive effects. Regarding exposure, Mr. Jaques stated that the information presented in the submission's exposure assessment was adequate to evaluate exposures from all anticipated sources. He noted that benzene exposures have been declining for many years and are expected to continue declining in the future. He used a flip chart to show the exposure range from less than 1 ppb to 10 ppb, and he pointed out where the estimates of food/water, outdoor air, indoor air, and the EU painting scenarios would fall. Food and water fall below 1 ppb, with the other scenarios falling within the range. He also noted that the RIOPA (Relationships of Indoor, Outdoors, and Personal Air) estimates fall within this range (Kwon et al., 2006) and said that, at the high end, it is the indoor sources of benzene that drive the indoor values, not the outdoor sources of benzene. Mr. Jaques concluded his remarks by stating that the benzene sponsors had not identified any data needs for benzene in the areas of hazard or of exposure.

8.1.1 Clarifying Questions from the Panel

One panelist asked if the sponsors had considered conducting studies in which they monitored biomarkers at low-dose exposures. He thought such studies might be useful in identifying any biological effects that benzene might cause at exposures approximating those occurring during daily activities. He noted that at the present time we do not know what the correct biomarkers would be, although some work has been done showing that benzene binds covalently to some proteins at low doses. He also mentioned benzene work done recently on the glutathione derivative of mercapturic acid. The presenter responded that the sponsors had not considered conducting work to monitor biomarkers at low-dose exposures.

In response to a panelist question regarding the scope of data needs to be identified and discussed, the panel Chair noted that the panel members were free to suggest data needs that were not included in the toxicity studies listed in the three VCCEP tiers. The Chair explained that for past VCCEP submissions,

EPA considered the comments of the individual panelists, together with the sponsors' submission and other data in determining what additional information, if any, should be obtained to adequately characterize the VCCEP chemical's risk to children.

8.2 Panel Discussion of Data Needs

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

> *13. 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.*
>
> *14. 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 panel Chair invited the panelists to identify items that they considered to be data needs and briefly explain why these items were needed. He explained that in the context of the VCCEP pilot program, *data gaps* are defined as areas that could benefit from additional data, additional analysis, or clearer presentation, while *data needs* are defined as data gaps requiring additional work before the potential risk to children can be adequately characterized. Not all data gaps are data needs, and the panelists may consider the risk characterization results when determining whether a data gap is a data need.

Exposure

Several panel members did not identify any exposure data needs; however, they did identify and discuss a number of exposure data gaps. Many of the items these panelists considered to be data gaps were classified as data needs by other panel members.

About half the panel members identified one or more data needs for exposure. The needs they identified included a more complete description of the process used to define benzene sources, better characterization of potential high-end exposures, more quantitative analysis, quantification of indoor air concentrations independent of outdoor concentrations, reconciling of exposure estimates from modeling with biomonitoring data, and the need to identify AML pediatric patients.

One panel member identified a need for the authors to describe more completely the process they used to define benzene sources. She noted that during the course of the meeting panelists identified information that appeared to be overlooked, for example, information about consumer products containing benzene. In addition, the higher exposures in Alaska were estimated by review of indoor air concentration data and the benzene content of Alaskan gasoline. These two factors raised doubts for her on the comprehensiveness of the search for benzene sources. In addition, she said the search for outdoor sources could be broadened to include mobile sources of benzene. She thought that a thorough search for benzene sources, identification of subpopulations exposed, exposure media (e.g., air, water, food), and frequency and intensity of exposure is needed, and the submission should describe more fully how the search for benzene sources was done.

Several panel members thought that a better characterization of potential high-end exposures is necessary. The panelists discussed ways to address this need through additional data evaluation. One mentioned that more precise definitions and quantification of typical and high-end exposures to benzene are needed in air, especially with respect to the following microenvironments and pathways: attached garages, environmental tobacco smoke, in-vehicle air, and outdoor/ambient air. In particular, this panelist thought

that the ambient benzene data presented in the submission are not sufficient for analyzing risks to children for outdoor air. He said the submission is deficient in that the authors provided insufficient justification for looking only at monitors in counties or cities with the highest reported TRI (Toxic Release Inventory) emissions of benzene, or for limiting their reporting to a single year (2003). Moreover, he said the submission gave no consideration to uncertainty in the estimates. The analysis and reporting of outdoor concentrations were superficial, and the rationale was not well articulated. This panelist also thought that the discussion and quantification of high-end indoor concentrations associated with attached garages and environmental tobacco smoke was deficient in terms of rigor, particularly with regard to generalizing the available data to regions or to the entire United States.

Another panelist mentioned the need for additional evaluation of benzene-containing consumer products and exposure patterns to determine whether there are additional subpopulations, other than Alaskans, with exposures higher than the high-end exposure defined in the submission. These might include exposures from small engine use, hobbies and crafts, or incense use. The panelist noted that while the benzene concentrations might be low, total exposures could be significant if frequency and intensity of use are high.

Two panel members identified the need for more quantitative analysis of the exposure assessment to consider explicitly the lack of knowledge resulting from limited data. One indicated that at least an uncertainty or sensitivity analysis is needed, if not a full probabilistic or stochastic assessment. Panelists noted that a probabilistic exposure assessment would be helpful to provide a more complete and explicit assessment of the distribution of exposure experienced by children, prospective parents and fetuses. Exposure pathways that do not contribute significantly to risk would not need to be carried through the probabilistic analysis. Panelists thought that data available for the benzene inhalation pathway should be sufficient to examine variability and possibly uncertainty in exposure estimates. A third panel member considered this item to be a data gap, but not a need, but suggested that distributional analyses be used whenever possible. He added that a sensitivity analysis can be useful by identifying the sensitive parameters. This information can then be used to design studies or conduct “data mining” to reduce uncertainty. One panel member pointed out that often in risk assessments, uncertainty is explicitly incorporated on the hazard/toxicity side of the risk characterization through the use of uncertainty factors; however, on the exposure side, it is not explicitly dealt with and it should be addressed.

One panel member identified the need to reconcile exposure estimates from modeling sources with the existing human biomonitoring data reported by Sexton et al. (2005) and Ashley (1994). The panelist noted that there is a lack of consistency between exposure estimates calculated from biomonitoring studies and exposure estimates calculated by modeling source and environmental measurements. She said this is troubling because it suggests the exposures used in the submission’s risk assessment may be underestimates, and it raises uncertainty about unidentified major sources of exposure. She said this lack of consistency remains important even after considering hazard because the submission’s calculated risk estimates are within the range of concern. Concerned that the steady state model used may have produced underestimates of benzene exposures, the panel member identified the need for the authors to back-calculate from the benzene blood levels reported by Sexton et al. (2005) and Ashley (1994) using a non-steady-state PBPK model and estimate the exposures required. The panel member also identified a need to obtain NHANES III data and use cotinine and benzene measures (and age) to characterize exposure distributions for smokers/nonsmokers and for various age groups. The panelist suggested using the distribution of values in non-smokers to approximate distribution of exposures (noting that variation in blood levels will be explained by variation in exposure plus metabolism).

Two panel members identified the need to develop an American AML-pediatric registry or database that would identify all cases. They said that doing this would allow for an historic exposure assessment, although it was recognized that dose-response information would not be obtained. One of the two

members also suggested that pediatric AML patients' bone marrow tissue samples might be studied. The panel briefly discussed whether further epidemiology studies might be useful; however, no panelist identified additional epidemiology studies as a data need. Other panelists noted that the half-life of benzene in blood is less than 24 hours and also that there is no true non-exposed reference group to use for human studies because the entire population is exposed to low levels of benzene.

Dr. Jeff Lewis, an observer from Exxon-Mobil Biomedical Sciences, informed the panel of a recent case-control study by Raaschou-Nielsen et al. (2001) that used the Danish Cancer Registry to examine benzene exposure during pregnancy and risk of childhood leukemia. The study examined risk for all leukemias combined and for AML cell types (ANLL specifically) for benzene exposures estimated based on traffic patterns and street configurations at the residences of cases and controls from 9 months before birth. No relationship between benzene exposures and any leukemia cell types was found. Dr Lewis brought this study to the panel's attention based on panelist discussions suggesting that there had been no high quality pediatric leukemia registry studies, and that no studies other than Shu et al. (1988) had examined prenatal benzene exposures in relation to the leukemia cell type caused by benzene exposure in adults (AML). He also noted that a literature review has just been published regarding studies of childhood cancer (including leukemia) and air pollution exposures (Raaschou-Nielsen and Reynolds, 2006).

One panelist said he did not believe the submission adequately quantified indoor air levels of benzene independent of outdoor levels. The panelist considered this lack of independent quantification to be a data need and stated that the submission should be consistent with scientific knowledge about indoor-outdoor relationship for benzene.

Panel members identified *data gaps* in the exposure areas as well. One suggested that the authors examine data on the incidence of AML in Los Angeles County and Harris County, Texas (the submission's source for the highest ambient benzene measurements) and relate these data to exposures to benzene for adults and children. In addition, he recommended that the authors consider harmonizing the construction and presentation of high-end exposures (e.g., the Texas, Minnesota, and Alaska levels) to make them more comparable. Continuing the monitoring of the US population's benzene blood levels was identified as a data gap by another panelist.

Additional areas identified as data gaps by panel members included further division of the 6-16 age group to account for teen smoking, occupational exposures to working adolescents, use of small engines, and the refueling scenario. In addition, one panel member also identified data gaps for exposure to incense, car interiors, painting, as well as exposure to potential parents working in additional occupations, such as toll booth workers or as bus drivers. Another member noted that the consequences of benzene exposures experienced by the various age groups will be easier to understand if biomarkers can be developed. This panelist also thought evaluation of outdoor air levels using RIOPA data and comparing levels with the current submission is a data gap.

Hazard and Risk Characterization

Several panel members did not believe there are any data needs with regard to hazard for benzene. They noted that all but one of the standard toxicity assays listed in the three VCCEP tiers are available, and the missing study (a 2-generation reproduction toxicity study) is not needed because such a study would be unlikely to lower the BMCL by more than 3-fold. One also noted that the human data are sufficient to characterize hazard and use of default uncertainty factor of 30 (10 for within human variability and 3 for incomplete database) for the non-cancer value as well as the linear dose response approach for cancer are appropriately conservative. Another panelist did not think additional animal studies are needed when humans are not showing an effect at all from low exposures.

While every panel members agreed that no additional standard bioassays from the VCCEP tiers were needed, some members identified additional toxicity work needed to characterize adequately the risk to children. Panel members identified data needs in the areas of development of an effective animal model, ADME data at different life stages, further work to understand mechanism of action, development of biomarkers from low level exposure, and development of dose-response data. One panelist said evaluating possible immunosuppression following dosing at various life stages would be useful to provide information to reduce the uncertainty factor related to child susceptibility.

The panel discussed the need for developing an appropriate animal model that mimics human disease in order to address questions regarding how benzene induces AML in humans and whether there is a differential susceptibility between young and old animals and humans. One panel member pointed out that a good animal model might allow the antecedent steps to bone marrow depression to be identified and the relative sensitivity of children versus adults to be tested. Another said a good animal model is needed to provide dose-response data for both adults and children. One panel member suggested that transgenic, knock-in, and knock-out mice were prime candidates for an animal model. Another panel member noted that it may take many years to develop an animal model for AML, and AML might not be the only effect of concern from benzene exposure.

A few panel members pointed out that this increased knowledge would not likely improve safety; rather it will improve certainty in the risk estimates. For example, appropriate animal data might provide a rationale to reduce the uncertainty factors used for non-cancer risk assessment, and this might result in raising the safe dose; likewise, additional information might result in the use of less conservative extrapolations and a resulting lower cancer risk estimate. Because of the low estimated exposures, several panel members did not think additional toxicity data were needed, and one voiced concern regarding the potential for using many laboratory animals. However, another panel member noted that if one used the high-end cancer estimates (EPA's linear based value), it would not take much additional exposure to reach a risk estimate within a range of concern, and the exposure assessment might not have captured the true high-end exposure.

Several panel members noted the need for ADME data for different life stages: the fetus/embryo, immature and adult laboratory animals. There is a special need to know the metabolism of benzene in the bone marrow of juvenile animals. A comparison of hematotoxicity by life stage also is needed: fetal vs. adult, newborn vs. adult, and adolescence vs. adult. A panel member noted that CYP2E1 is known to be an important factor in benzene's metabolism, and this enzyme is immature in the first several months of life. However, she thought well-designed animal studies to assess potential for age-related differences in bone marrow metabolism of benzene on hematopoietic toxicity are a data gap, not a data need.

The incomplete understanding of benzene's mechanism of toxicity was a concern to many panelists, and several considered it a data need. Specific suggestions included mechanism of action studies on hematotoxicity and genotoxicity (especially during development) and more research in bone marrow of immature and adult laboratory animals. One panel member noted that the current evidence to support a threshold for cancer is inadequate because benzene's mechanism of action is not known. Other panel members said that an understanding of benzene's mechanism of action was required to clarify the relationship between benzene-induced hematotoxicity and effects of anti-neoplastic agents.

One panel member explained that in the absence of a more complete database on the mechanism of benzene-induced bone marrow damage, the significance of the exposure assessment and the accuracy of the risk assessment are both somewhat limited. He presented an extensive list of data needs consisting of additional studies on the mechanism of benzene-induced bone marrow depression leading to aplastic anemia and benzene-induced myelodysplasia leading to acute myelogenous leukemia. He said that in theses studies appropriate emphasis should be placed on exploring the effects of benzene on the embryo,

the fetus and on children. Key issues will be time of exposure with respect to the developmental stage at which exposure occurs and the degree of exposure. (NOTE: This panelist provided additional details in writing, which are found in Appendix E.)

Another panel member noted that designing a study to determine the results of early benzene exposures on adult onset of disease is not easy for any chemical. Just treating the animal *in utero* is not enough, one needs to treat post-gestation as well. In addition, too high of exposure levels results in embryos dying and therefore the most sensitive may not survive.

Panel members discussed a number of other data gaps, but did not consider these data needs. Several panel members were concerned that not enough is known regarding the possibility that early life exposure to benzene causes or contributes to disease during adult life. One panelist identified a lack of data to understand the role of background metabolites (phenol, catechol, and hydroquinone) on benzene risk. These metabolites are found at higher background levels than the submission's estimated exposures. He also thought that work to characterize age-dependent expression of NQO1 is a data gap.

Other data gaps mentioned included identification of the hematotoxic mechanism of phenol-hydroquinone mixture and encouraging the Chinese investigators of the Hayes et al. study to monitor non-cancer endpoints (e.g., bone marrow depression and cytogenetics). Another panel member noted that additional human epidemiological studies with low-level *in utero* exposure could be done to assess the affect of benzene on the hematopoietic system, especially more "sophisticated" cell biomarkers. In addition, human developmental toxicity could be conducted to learn the significance, if any, of low-level benzene exposure in pregnancy on developmental outcomes.

Outside of identification of hazard studies, several panelists identified several other "data gaps." One panelist noted that it would be useful to have the submission vetted by an academic pediatric hematologist. He said one or more university-based pediatric hematologist/oncologists should be involved when questions regarding pediatric cancers are at issue. These clinicians are highly skilled and usually quite conversant with the human bio-medical literature that pertains to pediatric cancer causation as well as issues of chemical carcinogenesis ion pediatric patients. Two panel members also would like to see the use of the European Union POD more fully justified and for the assessment to consider selecting another POD, such as the non-cancer NOAEL.

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