Report of the Peer Consultation
Meeting on Xylenes

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

December 13 and 14, 2005
Erlanger, Kentucky

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

February 23, 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 toxicology, exposure, risk assessment, and children’s health met on December 13 and 14, 2005, to conduct a peer consultation of a submission on the xylenes [m-Xylene (CAS No. 108-38-3), o-Xylene (CAS No. 95-47-6), p-Xylene (CAS No. 106-42-3), and Mixed Xylenes (CAS No. 1330-20-7)]. 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 xylenes to children, and if not, to identify data needs.

The sponsors and their contractors provided the panel with presentations consisting of a general introduction and summaries of the sponsors’ assessments of hazard, exposure, risk characterization, and data needs based upon material in their written document. They noted that the three xylene isomers are treated as a single category because of similarities in their biological activity and chemistry. Data are presented on both individual xylene isomers and also on isomer mixtures.

In summarizing the hazard assessment, the presenter discussed toxicity data addressing the endpoints in the three VCCEP tiers and stated that the xylenes are not acutely toxic by any exposure route. They are not carcinogenic or genotoxic and are unlikely to be immunotoxic. Subchronic effects consist primarily of changes in liver and body weights. Developmental toxicity is largely confined to doses inducing maternal toxicity, and no reproductive toxicity has been found. Metabolic profiles are similar in animals and in humans. Neurobehavioral effects are considered to be the critical endpoints in both adults and offspring.

Several panelists expressed concern regarding the lack of information from exposures to children or from direct xylenes dosing studies in young animals. They said data on internal doses and metabolism were especially needed. Others wanted more information presented on the differences in distribution, metabolism, and excretion that might exist between humans and laboratory animals and in the magnitude of variation among humans. Some members wanted to see human toxicity data from intentional solvent abuse situations or unintentional excessive exposures. One panelist said more information on pulmonary metabolism was critical for the xylenes because inhalation is the major route of exposure, and xylenes metabolism by pulmonary tissue differs from its metabolism by hepatic tissue. Panel members expressed differing views of whether the animal reproduction studies or neurotoxicity studies were more sensitive in detecting xylenes toxicity. Many panelists concluded that multi-generation studies on xylenes were not needed because other studies were available to address reproductive and developmental toxicity. Other panel members said neurobehavioral development was a concern because there were no data from direct dosing during the neonatal and post-natal period to address this endpoint. Panel members generally supported the approach used to derive the acute and chronic health benchmarks; however, some expressed concern over the limited toxicity database supporting the benchmarks.

The sponsor’s summary of the exposure assessment explained that the target populations were considered to be children in four age groups as well as prospective mothers. The assessment
included inhalation, ingestion, and dermal exposure routes. Exposure data were presented as typical (average or mean) or high-end (90th or 95th percentile) values. For exposures from consumer products, the sponsors assumed that the label’s directions for product use were followed in both typical and high-end situations. The inhalation pathway is the primary route of exposure, except for infants nursing from occupationally-exposed mothers.

Several panel members questioned the assumption that all consumers followed usage directions for products containing xylenes. Many others said the target population of children should have been divided into more than four age groups, and they especially disagreed with placing all children less than one year of age into a single group. Panelists said that the fate of xylenes in neonates and children as a result of direct exposure was unknown because no studies involving the direct dosing of young animals had been conducted. They thought use of available dosimetry modeling techniques to assess life-stage dependent changes had not been not fully explored.

Some panel members thought the exposure assessment provided a thorough presentation of exposure sources. Others wanted more consumer products included, or, at a minimum, a more thorough presentation of the rationale used to select the consumer product scenarios that were presented. Some panel members also had concerns about whether the ambient xylenes levels and their use as the basis for calculating indoor levels would adequately represent population exposures in high traffic areas.

The risk characterization presentation discussed reference doses (RfDs) and concentrations (RFCs), as well as the parameters for defining health benchmarks such as the point of departure, the adjustment for human equivalent concentration, and the database uncertainty factor. Health benchmarks identified by regulatory agencies also were presented, and the chronic inhalation health benchmark identified by the sponsors was contrasted with the U.S. EPA’s RfC. The presenter concluded that short-term and chronic aggregate exposures are not expected to cause adverse effects to the general population, including infants and children.

Several panel members were not sure the sponsors’ selection of adjustment and uncertainty factors was justified, noting that the numbers chosen might be different if more data were available. Most members thought the Hazard Quotient (HQ) approach was correct to use for the xylenes, but said the HQ database was inadequate because nothing was known about the pharmacokinetics, metabolism, or sensitivity of children. Most panel members said the risks were adequately characterized for prospective parents and for the embryo and fetus, but not for nursing infants or for post-nursing infants through adolescence. Two panelists suggested expanding the scope of the risk characterization to include reasonably foreseeable misuse situations.

In the data needs summary, the presenter reviewed the hazard endpoints addressed for VCCEP Tiers 1, 2, and 3, and listed the specific studies conducted and their results. He noted all Tier 1 endpoints had been met for the xylenes, and toxicity data to address Tier 2 and 3 endpoints are available from the xylenes themselves or from similar aromatic hydrocarbons. He recommended no further toxicity testing of the xylenes. Regarding exposure, he said inhalation is the major exposure route and ample measurements of ambient and source-specific air concentrations exist. In addition, the air concentrations of xylenes are adequately regulated under numerous environmental and health regulations. He recommended no further exposure measurements or
studies of xylenes. The presenter concluded that the risk characterization of xylenes indicates a low potential for adverse health effects for all the target populations and no data needs exist for these chemicals.

Panelists were polled individually to identify items they regarded as data gaps or data needs. Numerous items were identified in both categories. The most common data needs identified were (1) to obtain additional ADME and pharmacokinetic information relevant to children, and (2) to divide the children’s birth-to-one-year age group into separate groups and conduct separate assessments on each subdivision. The most common data gaps listed were (1) to determine pulmonary metabolism and compare it to hepatic metabolism, and (2) to provide more hazard, exposure, and risk characterization information on the xylenes mixtures.
1. Participants

Sponsor

American Chemistry Council Benzene, Toluene, and Xylenes VCCEP Consortium, of which the following companies are xylenes sponsors: BP, Chevron Phillips Chemical LP, ExxonMobil Chemical Company, Flint Hills Resources, LP, Marathon Petroleum LLC, Shell Chemical LP, Sunoco, Inc., Total Petrochemicals U.S.A.

Presenters

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Robert Wood Johnson Medical School and Rutgers University

**NOTE:** 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.

**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 xylenes assessment was submitted by the American Chemistry Council Benzene, Toluene, and Xylenes VCCEP Consortium, of which the following companies are xylenes sponsors: BP, Chevron Phillips Chemical LP, ExxonMobil Chemical Company, Flint Hills Resources LP, Marathon Petroleum LLC, Shell Chemical LP, 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/childhlt.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 has 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 risk characterization and a data needs assessments.

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 Tier 2 or 3. The Benzene, Toluene, and Xylenes VCCEP Consortium volunteered to sponsor a Tier 1 assessment for m-xylene (CAS No. 108-38-3), o-xylene (CAS No. 95-47-6), p-xylene (CAS No. 106-42-3), and mixed xylenes (CAS No. 1330-20-7).1 Data links to the submission document and appendices are available to the public on the Internet at http://www.tera.org/peer/VCCEP/xylenes/xylenesWelcome.html. If data needs are identified through this process, the Benzene, Toluene, and Xylenes VCCEP Consortium will decide whether to volunteer for any additional data generation or testing and whether to provide a Tier 2 assessment for VCCEP peer consultation.

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

The VCCEP Peer Consultation Panel for the xylenes consisted of 12 members independently selected by TERA. Each panel member disclosed information regarding potential conflicts of interest and biases for the VCCEP program in general, or for the xylenes 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, pediatric medicine, and children’s health. The panel received a copy of the submission and key references approximately one month before the meeting, so that they had adequate time to review the documents and prepare for the discussions. Panel members bring a range of views and perspectives to the peer consultations, reflecting the interest in VCCEP by a wide range of

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1 Only m-xylene and o-xylene had been selected by the U.S. EPA to be VCCEP pilot chemicals. Subsequent to the publication of the list of pilot chemicals, the Benzene, Toluene, and Xylenes VCCEP Consortium proposed that p-xylene and mixed xylenes be included in the Xylenes assessment. The U.S. EPA agreed.
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 any 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 to the public on the Internet at

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 compilations. 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’ biosketches 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 had additions and changes. Dr. Hakkinen noted that the
ACC’s Exposure Assessment Task Group he had previously chaired was involved in funding a
study cited as a reference (Murray and Burmaster, 1995) in the sponsor’s xylenes submission.
Dr. Christopher stated that several years ago he had received payment from ACC for reviewing a
proposal for PBPK work (Krishnan and Pelekis, 1995) included in Appendix C of the sponsor’s
xylenes submission. Both Dr. Hakkinen and Dr. Christopher said they did not consider their
disclosure additions to be conflicts of interest, but they were disclosing them to assure
completeness. Dr. Miller noted the possibility that some work on xylene chemicals might have
occurred at CIIT during the time he was employed by that organization, but, if so, he was not
personally or directly involved. Dr. Cohen Hubal noted that she was a member of the ACC
Human Exposure Assessment Technical Implementation Panel, but it has not been active for several years.

Three sets of written public comments regarding the xylenes were 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.

**NOTE: in the following presentations and discussions, unless otherwise noted, the term “xylenes” means the three individual xylene chemicals alone and also these three chemicals together in a mixture.**

### 4. Sponsor Introduction

Mr. Andrew Jaques of the American Chemistry Council briefly described the company membership of the Benzene, Toluene, and Xylenes VCCEP Consortium. He outlined the presentations to be given during the meeting and provided the background for the inclusion of the xylene chemicals in the VCCEP pilot program. Mr. Jaques stated that the three xylene isomers are being treated as a single category because of their similar biological activity and chemistry. He noted that data are presented on individual xylene isomers when available; however, in many cases the data are on xylene mixtures. The mixed xylenes are a complex petroleum product that contains the three xylene isomers plus ethylbenzene in varying amounts. See Appendix D for Mr. Jaques presentation slides, which provide further details.

### 5. Hazard Assessment

#### 5.1 Sponsor Presentation

Dr. Ceinwen Schreiner, a consultant to the VCCEP Consortium, summarized the hazard data presented in the sponsor’s submitted assessment (see Appendix D for her presentation slides, which provide further details of her presentation). She explained that evaluating the xylenes as a single category is justified because the three isomers demonstrate similar physical and chemical properties, present similar hazards and potential health effects, and have similar sources of exposure. The VCCEP hazard endpoints are addressed by toxicology data available on individual isomers and on isomer mixtures. In humans, acute exposures to xylenes are known to produce irritation and a range of CNS effects. Information on subchronic and chronic effects in
humans is limited because of insufficient characterization of exposure and simultaneous exposures to other chemicals. The metabolic profiles of the xylenes are similar in animals and humans. Dr. Schreiner summarized the hazard information available to address the VCCEP Tier 1, Tier 2, and Tier 3 endpoints (details of the studies on each endpoint are listed on the presentation slides). She emphasized that the existing data address all Tier 1 endpoints, as well as most Tier 2 and Tier 3 endpoints. Dr. Schreiner stated that the xylenes are considered non-toxic when administered to laboratory animals acutely by the oral, dermal, or inhalation routes. They are not carcinogenic or genotoxic and are unlikely to be immunotoxic. Subchronic oral dose effects seen in laboratory animals are primarily changes in liver and body weights. No reproductive toxicity was found in a one-generation study in rats. Evidence of developmental toxicity in laboratory animals is largely confined to doses inducing maternal toxicity. Neurobehavioral effects are critical endpoints in laboratory studies with both adults and offspring; however, developing offspring are not more sensitive than adults to the neurotoxic effects of xylenes.

5.1.1 Clarifying Questions from the Panel

Asked what specific data are available on direct xylenes dosing to juvenile animals or on effects in exposed children, the presenter responded that no studies were found in which animals were dosed directly with xylenes from birth or from weaning to adulthood. Information on exposed children was very limited. A one-generation study in rats exposed offspring to xylenes in utero via the dams and then via milk (API, 1983). The sponsors considered the offspring’s exposure to xylenes in utero and then via milk to be at least as rigorous as exposing young animals directly to xylenes from post-weanling to adulthood. The presenter added that this conclusion is supported by extrapolating results of multi-generation studies on solvent materials similar to xylenes (McKee et al., 1990; Roberts et al., 2003). The presenter said that, taken together, the results of all reproductive and developmental studies support the conclusion that developing and young animals (prenatal, postnatal, and post-weaning to maturation) are not more sensitive to the adverse effects of xylenes than are adults. In further discussion of the one-generation study, the panelists and presenters noted that this 1983 study would not meet current guidelines for a one-generation study. In particular, they noted that the amount of xylenes the pups ingested from the dams’ milk was not determined. Also, the dams were not washed upon removal from the inhalation chamber, so their fur was a potential source of direct xylenes exposure for the pups (orally, dermally, and via inhalation).

Other panelists asked if data on direct xylenes exposure to children had been obtained from Poison Control Centers, from occupational or product usage situations, from intentional solvent abuse situations, or from databases such as NHANES or birth registries. The presenter said very little information on children was found from these sources, and the available information was not definitive because of uncertainties regarding the amount of xylenes involved and concurrent exposures to other, non-xylene chemicals. Reference was made to section 6.1.2 Human Experience Summary of the submission document in which the known effects of xylenes in humans are listed. One panel member added that while human variability is often assumed to be about 10-fold, it really is more like 30 to 50-fold, which is supported by current California EPA studies of variation among children.
One member asked the presenter to explain the significance of biochemical changes noted in the brains of exposed animals -- changes that sometimes persisted after the exposure period ended. He added that people exposed chronically to mixed solvents may show neurotoxicity, but animal models for these human effects do not exist. The presenter responded that brain biochemical changes observed in animals are not always expressed as functional changes, and therefore their significance is unclear. The panelist and presenter acknowledged the difficulty in relating brain biochemical changes in animals to humans, and especially to children. The panelist thought that such changes in animals might be reflected in humans and might be the cause of some of the human neurotoxic effects associated with xylenes exposure. He thought that the significance of this effect for children should be explored further.

Although they were not strictly clarifying questions, several panel members identified relevant information they considered missing from the document or made other comments. These items are summarized as follows:

- Impairment of color discrimination is the most sensitive indicator of mixed solvents toxicity, so it may also be a sensitive endpoint for xylenes. A discussion of this endpoint should be added to the hazard assessment. Also, recent reports of ototoxicity in humans are not included in the hazard assessment. The sponsors responded that the hazard assessment was drafted before the ototoxicity reports were published, and they will consider adding these recent reports.

- The hazard assessment notes the finding of cleft palate in developmental studies from the early 1980s, and it ascribes this lesion to stress. A panelist agreed that stress was the likely cause of this lesion; however, he said stress also causes other types of developmental effects (e.g., wavy ribs). If these other lesions were observed, they should be presented and discussed because their occurrence gives credibility to attributing the cause of the cleft palate to the stress of the experimental procedure rather than to the chemicals themselves. The presenter responded that wavy ribs were reported in some studies, but their finding was not considered definitive because it resulted only from a continuous 24-hour exposure period not representative of human occupational or product-use situations. The panelist thought that findings from a 24-hour exposure period in a rodent study should not be discounted automatically. Also, he recommended that the hazard assessment state whether the fetal examinations for terata were external only, skeletal, or visceral examinations. He explained that these are distinctly different procedures and would provide meaningful information.

- Two panelists questioned the presenter regarding the meaning of the term “adaptive” metabolism when referring to children. They said that a response that might be considered to be adaptive (rather than adverse) in adults might be adverse in children because of their developing enzyme and organ systems. They asked what was required for an “adaptive” enzyme response in children to be considered “adverse.” A sponsor replied that the term “adaptive” was taken from the literature reports and was used only in the context of studies on adults. They agreed with the panel members that the meaning of this term was unclear in respect to enzymatic changes in children. Another panelist added that the enzyme changes considered adaptive relative to an adult’s metabolism of
the xylenes also would affect the metabolism of endogenous steroid hormones. He wondered whether a change that impacts endogenous steroids should ever be considered adaptive (rather than adverse) in adults, and especially in children. He recommended that a discussion of this point be included in the document.

- One member disagreed with the document’s statement of “no evidence of increased susceptibility to developing organisms.” He thought the statement should be restricted to say “in utero” because no data were presented to assess the (possibly increased) susceptibility to direct xylenes exposure in the time period directly after birth.

5.2 Panel Discussion of the Hazard Assessment

The panel discussion of the hazard assessment addressed two charge items:

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 a) to the prospective parents, b) to the embryo and fetus, c) to the nursing infant, and d) to post-nursing child through adolescence to the age of sexual maturation.

2. Discuss whether the quantitative hazard and dose-response parameters used (e.g., RfD, RfC) are appropriate for the xylenes.

5.2.1 Available Hazard Information

Responding to this charge item, several panel members expressed concern regarding the lack of information on effects of children’s exposure or from direct dosing of young animals. They said data on internal doses and metabolism were especially needed. Panel members also wanted the hazard assessment to discuss the differences in distribution, metabolism, and excretion that occurs between humans and the tested animal species, the magnitude of human variation in distribution, metabolism and excretion, and also whether the toxic chemical moiety was the parent molecule or a metabolite. One member said that knowing half-lives in differing age groups is essential for interpreting results from the rotorod study, which was presumed to be done 24 hours post-exposure. If xylenes were completely eliminated from the body at 24 hours, the rotorod effect would be a sign of residual damage, and therefore of added significance.

One panelist stressed the importance of understanding how human genetic variability affects pharmacokinetics within the target populations. He explained that polymorphisms in key enzymes, such as CYP2E1 and the glutathione enzyme system, might substantially impact human pharmacokinetics; therefore, relying on data from laboratory animals might not be sufficient. Another member said that because human enzymatic detoxification pathways develop with increasing age during childhood, further discussion relating xylenes metabolism and disposition to age should be provided. He noted that the sponsor’s document mentions CYP2E1, but it fails to include the reports by Ginsberg et al. (2004a,b) on the pharmacokinetic differences between children and adults. The sponsors replied that 95-98% of xylenes are oxidized to hippuric acid and the remainder is exhaled as parent compound. Panelists responded that this
metabolism was from human adults, but data from young children were not available, nor are there data from subpopulations that might have enzyme deficiencies. Another member added that further uncertainty is caused by the lack of understanding of how rodent neonates relate to human infants. He said substantial differences exist between these species in the maturity of organs and tissues at birth. For example, the blood-brain barrier develops before birth in humans, but after birth in rodents. Differences such as this can be significant in extrapolating the observed effects in rodents to humans.

A panel member noted the submission does not include a section on pulmonary metabolism, and xylenes metabolism in the lung is likely to differ from its hepatic metabolism. He thought that knowledge of pulmonary metabolism is critical for the xylenes because inhalation is the major route of exposure. Some panelists noted that dosing via inhalation shows lower effect levels than dosing via ingestion. This suggests first-pass hepatic metabolism may occur. Other panelists noted the submission document contains information comparing young and adult rat livers, and the relationship between oral and dermal dosing is presented in the PBPK models in the document’s Appendix C. One panelist criticized Appendix C for not providing sufficient data on children less than one year of age. He thought statements in the document’s text indicating no adult-child differences in the internal concentrations of xylenes from inhalation exposures were inconsistent with data presented in Appendix C and elsewhere in the document. He said age-dependent dosimetry models are available and should be more fully explored.

Panelists also were concerned about the lack of data on potential dermal absorption from children’s use of consumer products. One member acknowledged the NHANES III (U.S. DHHS, 2000) data on blood levels of xylenes, but wanted more information provided on children. She also said more information should have been provided on the effects of xylene abuse because that would aid in hazard identification.

When asked by the panel Chair about the need for a two-generation development study on xylenes, two members replied that such a study would not provide meaningful additional information to what was already known from the xylenes one-generation study and from multi-generation studies on toluene, ethyl benzene, and aromatic naphtha chemicals. They said multi-generation studies are not designed to assess the sensitive neuro-developmental issues that appear to be the critical toxic effect for xylenes.

Panel members expressed differing views of whether reproduction studies or neurotoxicity studies were more sensitive in detecting xylenes toxicity. Some were concerned that subtle neurotoxic effects might occur at low doses or from long durations of exposure. They wanted to know how to relate changes observed in human brain biochemistry to functional effects seen in animals (i.e., rotorod studies). One member explained that human effects are first seen in the cerebrum and brain stem, while the rotorod studies measure effects on the cerebellum. Some thought biochemical changes might be precursors of performance impairment. Two members were not convinced that the data reflected the most critical effect – particularly given uncertainties in implications of neurochemical changes, absence of data on internal doses with age, and toxicodynamic differences in postnatal neurological development. Panel members acknowledged that because they were not certain the most critical endpoint had been identified, they would rely on the weight of the evidence.
5.2.2 Hazard and Dose-response

The panel discussion of this charge item focused on the benchmarks used to characterize the adverse health effects of xylenes (described in Section 8.1 of the sponsors’ document, beginning on p. 142). One panelist thought the parameters used by the sponsors were correct, but he said the mixing of approaches and models was sometimes confusing. Other members took a different view, saying they appreciated the different options presented in the document. They noted that several different studies might have been chosen for the point of departure for the chronic RfC and also that different uncertainty factors might have been selected. Panel members generally supported the manner in which the acute inhalation, chronic inhalation, and chronic oral health benchmarks were derived; however, some expressed concern over the toxicity databases supporting these benchmarks. They thought most of the toxicity studies were dated, the longer-term studies tended to be oral rather than via inhalation, and no studies were available that directly dosed young animals.

6. Exposure Assessment

6.1 Sponsor Presentation

Ms. Julie Panko, a consultant to the VCCEP Consortium, summarized the exposure data presented in the sponsor’s submitted assessment (see Appendix D for her presentation slides, which include further details). She noted the exposure assessment took into account the existing health benchmarks for the xylenes. Exposures were assessed for prospective mothers (aged 19-35 years) and for children in four age groups based upon their activity patterns: less than 1 year, 1-5 years, 6-13 years, and 14-18 years. Fetal doses were not quantified because the xylenes were not considered to be teratogenic or to affect the embryo or fetus adversely. The assessment included inhalation, ingestion, and dermal exposure routes. Exposure sources were placed in one of three categories: chronic background, chronic source-specific, or short-term episodic source-specific. Background exposure included indoor and outdoor air and dietary exposures from food, water and breast milk. Source-specific exposures included tobacco smoke, gasoline, consumer products and occupational exposures. Exposure data were presented as typical (average or mean) or high-end (90th or 95th percentile) values. For exposures from consumer products, the sponsors assumed that the labeled directions for product use were followed in both typical and high-end situations. Specific exposure values for all the sources and population groups are summarized on the presentation slides, together with the assumptions used in compiling the data. The exposure assessment demonstrates that the inhalation pathway is the primary route of exposure. Systemic (absorbed) doses from inhalation are at least one order of magnitude higher than those resulting from oral ingestion or dermal pathways, except for infant ingestion of breast milk from occupationally-exposed mothers. For typical chronic inhalation exposures, indoor air contributes the most. For high-end chronic inhalation exposures, occupational situations contribute the most.

The sponsors’ choices of the critical toxicity study and uncertainty factors are discussed further under Charge Item 7.
6.1.1 Clarifying Questions from the Panel

A member asked whether the U.S. National Library of Medicine’s Household Products Database had been used and listed several consumer products with very high xylenes content (up to 80% of product) from that database. He asked if these had been considered in identifying the reasonable worst-case scenarios for children’s exposures. The presenter responded that they had looked at this database and had concluded that it contained the same products as the other databases they used. She noted that all xylene-containing products were considered, and the scenarios represented reasonable worst-case exposures exceeding the exposures expected to occur from using products that contain the highest xylene concentrations. The member also asked whether dermal exposures were considered during product use. The presenter replied that dermal absorption during product use was not considered a significant source of exposure because xylenes are highly volatile under non-occluded skin contact conditions, such as would be expected to occur. Another member added that dermal penetration could occur in skin contact times as short as 14 minutes.

Responding to questions from several panelists, the presenter explained the rationale for calculating an indoor-to-outdoor delta value to derive representative indoor xylenes concentrations. The sponsors used this approach to estimate indoor air concentration in regions of the country where indoor air concentration measurements have not been reported. The presenter also explained the sponsor’s decisions for selecting specific reports of exposure data (e.g., Adgate et al., 2004) for the tables in the Exposure Assessment (Section 7) of the document. Some members responded that outdoor xylenes concentrations also were important because they might be elevated in areas near mobile point sources (e.g., near busy highways), as well as near stationary sources (e.g., manufacturing plants). Also, the data obtained from PAMS (Photochemical Assessment Monitoring Stations) in regions of ozone non-attainment are usually not representative of the air at ground level directly outside buildings. This is because the PAMS monitors usually are located on the roofs of buildings and therefore might provide lower values than exist at ground level.

Several panelists questioned the sponsors’ assumption that consumers would follow usage directions for products containing xylenes. One member said studies have shown up to 41% of consumers ignore the usage and ventilation instructions on products, and young children usually had no choice in whether the instructions were followed by the product user. The sponsors acknowledged they had struggled with the best assumptions to use in estimating exposures from consumer products, especially the high-end exposures. They explained that many variables had been considered, including the amount of product used, the usage duration and frequency, the room size, the type and amount of ventilation, and the likely correlations between these factors. They said that the scenarios presented were reasonable worst-case situations. The scenarios did not assume the maximum possible exposure from each one of the variables because doing so would result in unrealistic situations, for example, a high end user would likely use ventilation to reduce objectionable chemical odors.

6.2 Public Comments on the Exposure Assessment

Prior to the meeting, two sets of written public comments regarding the exposure assessment had been submitted to TERA from scientists at the U.S.EPA, and one set of written public comments...
had been submitted by a VCCEP Core Panelist who was unable to attend the meeting. These comments were summarized and the panel was instructed to consider the comments in their subsequent discussion of the exposure assessment. (Copies of the written public comments are located in Appendix C.)

6.3 Panel Discussion of the Exposure Assessment

The panel discussion on Exposure Assessment addressed four charge items:

3. Discuss whether the fates of these chemicals are adequately understood, both in the environment and within the human body.

4. Discuss whether the available data are adequate regarding the following exposure aspects: sources, routes, frequency, duration, and intensity.

5. Discuss whether all time periods relevant to childhood exposure have been adequately and correctly evaluated. These times consist of the following: (a) paternal and maternal exposure prior to conception, (b) prenatal development, (c) and postnatal development to the age of sexual maturation.

6. Discuss whether the estimates of exposure have been calculated appropriately and correctly.

6.3.1 Fate in the Body and Environment

Several panel members noted that the document contained essentially no discussion of the fate of xylenes in the environment, although it was noted that inclusion of such information may not be critical for this document. The sponsors responded that xylenes remaining in the environment are eventually oxidized. Regarding human exposure to environmental xylenes, systemic absorption is about 60% from inhaled xylenes and essentially 100% from ingested xylenes.

Several panelists pointed out that the fate of xylenes within the bodies of neonates and children as a result of direct exposure was unknown because no studies involving the direct dosing of young animals had been presented. Members discussed the likely internal doses, which would result from inhalation or oral exposures, with one panelist noting that data on first pass metabolism in the lung would be very useful. Others noted the issue of age-dependent differences in toxicokinetics needed further evaluation.

6.3.2 Adequacy of Available Data

The panel had a number of comments and questions regarding the exposure data and the manner in which the data were presented.

- Some members commented on the gasoline fueling scenario presented by the sponsors, saying that the assumed fueling duration of 3 minutes was unrealistically short. They noted further that infants in a vehicle with the windows down would be exposed to essentially the same concentration of xylenes as the fueler.
• One member asked whether probabilistic risk assessment could have been done for inhalation. The sponsors replied that the available data on indoor air concentrations were too limited to conduct a probabilistic risk assessment.

• Some panelists said it was difficult to identify whether modeling values or measured values had been used for various parameters and whether modeling values were higher or lower than measured values. The sponsors replied that modeling was done only for consumer products.

• Other members did not understand many of the tables (e.g., 7.5-7.6) and figures (e.g., 7.4-7.7) in the exposure section. They suggested providing more complete titles and legends to make the tables and figures capable of “standing alone.”

• Many panel members were confused regarding the classifications of “user” and “non-user.” The presenter explained that they considered everyone present in the “usage room” to be a user, and considered non-users to be people in other rooms.

• Others suggested providing a better explanation of how the frequency of repetitive, acute exposures occurring over a few days fits into the total picture.

• Some members did not understand why the use of consumer products was not included in chronic exposure values. The sponsors responded that they considered product-use situations to be more accurately classified as repetitive, acute exposures than chronic exposures. However, regardless of how they were classified, the contribution of consumer product usage was included in the total exposure values calculated for each target population.

• While a few panelists said they thought the document did a thorough job presenting sources of exposure, others said more consumer products should have been included and the reasons for choosing certain products and excluding others were not clear.

• Several panelists discussed the possibility of conducting modeling based upon body weights. They concluded that, although this might be done, basing the modeling on age was preferred because age correlated more closely with metabolic rate.

### 6.3.3 Time Periods Relevant to Childhood Exposure

Several panelists said the target population of children should be divided into more than four age groups, and they particularly disagreed with placing all children less than one year into the same group. The sponsors explained that they had grouped the children by activity pattern more than by age. Panel members pointed out that activity patterns vary markedly in children less than one year. For example, a crying neonate will have a much greater inhalation exposure (relative to body weight) than will a one-year-old. They said this difference is important because indoor air is a major xylenes exposure source. Others noted that xylenes are heavier than air, so depending on the degree of air circulation within the house, infants lying on the floor might have more xylenes exposure than toddlers or older children. Some members suggested using the same age groups for young children that are used by the U.S. EPA: birth to 1 month; 1 to 3; 3 to 6; and 6 to 12 months (U.S.EPA, 2002). While agreeing that additional break out of infant groups was a good idea, one member considered the scenario the sponsors presented of an infant nursing from an occupationally-exposed mother to be extremely health-protective and sufficient to account for the uncertainties of inhalation exposure resulting from not having a break out of infants less than one year. Others said the nursing scenario described was not overly conservative because many occupationally-exposed mothers used their expressed milk to feed their infants.
Two members expressed concern that the tables on pp. 100-102 use data only from one-year-olds (no one younger) to estimate the oral, inhalation, and dermal exposures for the age range of birth to one year. They noted that milk ingestion relative to body weight changes markedly during the infant’s first year of life, as do other factors impacting exposure such as milk fat content and the percentage of time the nursing mother stays at home.

Other members said more information was needed during the entire post-natal development period, and more information should have been provided on the behavioral changes occurring during pregnancy, which affect exposure of the woman and the fetus. One member added that the age of prospective mothers should begin at a younger age than 19 years.

6.3.4 Exposure Estimates

Prior to the meeting, a TERA staff member conducted a spot check of calculations in the document and found no errors. None of the panel members reported finding any errors in the exposure estimate calculations, although some members suggested more attention was needed to ensure consistency in the use of significant figures throughout the document.

One member said the data presented on the xylenes exposure from foods underestimated the real exposure because xylenes content of the food was considered to be zero when it was found to be below a certain cut-off concentration.

One panelist questioned the use and meaning of the inhalation absorption factor of 0.6 (labeled as ABSi), which is first defined on page 85 of the submission document and then used repeatedly in the subsequent text and tables in the exposure assessment section of the document. The presenter explained that the factor of 0.6 was needed to convert the amount of inhaled xylenes to a systemically absorbed dose expressed as mg/kg-day. This conversion allows the systemically absorbed dose from inhaled xylenes (which are 60% absorbed) to be compared directly to the systemically absorbed dose from ingested xylenes (which are 100% absorbed). Another panelist cautioned that the inhalation absorption factor for laboratory animals was not necessarily the same as for humans, and this must be considered when comparing inhalation exposures across species.

7. Risk Characterization

7.1 Sponsor Presentation

Dr. Abby Li, a consultant to the VCCEP Consortium, summarized the risk characterization data presented in the sponsor’s submitted assessment (see Appendix D for her presentation slides). Her presentation focused on reference doses and concentrations (RfDs and RfCs) and on the following key issues for a chronic health benchmark inhalation exposure: the point of departure, the adjustment for human equivalent concentration, and the selection of uncertainty factors. The AEGL (Acute Exposure Guideline Levels), RfD, and RfC health benchmarks identified by the U.S. EPA (2003) also were discussed, together with the toxicity data that served as the basis for
these Agency benchmark values. Dr. Li contrasted the chronic inhalation health benchmark identified by the sponsors with the RfC identified by the U.S. EPA (2006). She noted that differences existed in two adjustments or uncertainty factors that affected the benchmark calculation. First, the sponsors used a rat-to-human ratio for blood:gas partition coefficient of 1.7 rather than EPA default value of 1 in calculating the human equivalent concentration. Second, the sponsors used a database uncertainty factor of 1 rather than the EPA value of 3. Other aspects of the sponsors’ assessment, including the selection of the critical effect, and the selected inter- and intraspecies uncertainty factors were the same as for the EPA RfC. Details explaining the sponsor’s rationale for departing from the U.S. EPA values are listed in the presentation slides. Dr. Li presented the risk quantification methodology used by the sponsors for chronic background and source-specific exposures, and for consumer product exposures. She concluded that short-term and chronic aggregate exposures are not expected to cause adverse effects to the general population, including children.

7.1.1 Clarifying Questions from the Panel

In response to several questions, the presenter confirmed that the overall risk characterization and the bar graphs on chronic background exposures, chronic source-specific exposures, and consumer product exposures shown during the presentation included data from smokers and from hobbyists. High-end exposures also were included (defined by the sponsors as the 90th or 95th percentile values).

Some panelists questioned the sponsors’ conclusions on Slides 7-9 regarding the Point of Departure based on the studies of Korsak et al. (1992, 1994). They wanted to see more raw data from these studies before agreeing that 50 ppm was truly a NOAEL. The presenter responded that further data had been requested from the investigators, but no additional information had been provided. Another panel member expressed concern about the low statistical power from these studies because of small sample sizes.

Panel members said they were not confident that the sponsors’ decisions on which adjustment and uncertainty factors to use were really justified. They noted that the numbers chosen (1.7 for the rat:human ratio for blood:gas partition coefficient and 1 for the database uncertainty factor) might be different if more data were available, and also that regulatory agencies outside the United States had selected differing values for their xylenes risk assessments.

7.2 Panel Discussion of Risk Characterization

The panel discussion on Risk Characterization addressed three charge items:

7. Discuss whether the risk characterization appropriately integrates the exposure and hazard information for the xylene chemicals both individually and as mixtures.

8. Discuss whether risk characterization methodology employing a Hazard Quotient (HQ) approach is appropriate for the xylenes.
9. Discuss whether the risk characterization adequately characterizes the risk a) to prospective parents, b) to the embryo and fetus, c) to the nursing infant, and d) to the post-nursing child through adolescence to the age of sexual maturation

7.2.1 Integration of Exposure and Hazard Information

One member said that relevant uncertainties had not been presented for several items related to exposure, so it was not possible to determine if the hazard and exposure data were appropriately integrated. The presenter responded that no additional information on exposure uncertainties was needed because both typical and high-end exposures had been adequately characterized. She said including more data on indoor air exchange rates, additional consumer products, etc. would not affect the key uncertainties for any target population, except perhaps high-end occupational exposures. The panelist disagreed, saying more information was needed on such uncertainties, such as activity levels and subpopulations. Another member added that the risk assessment was driven by the high-end exposures, so such exposures, such as from working on cars and doing hobbies were important. He said it also was important to consider children as potential hobbyists and to add more about xylene exposure from mixtures.

Panel members discussed whether the three xylene isomers should be considered to have equivalent toxicity, as the document appeared to assume. They noted that one of the rotorod studies of Korsak et al. (1990) reported the isomer potency as $o$-xylene $> m$-xylene $> p$-xylene. This finding might be significant because another rotorod study by these investigators (Korsak et al., 1994) was selected as the critical toxicity study and used as the basis for calculating the point of departure for xylene. One member disagreed with the sponsors’ decision to use the Korsak et al. (1994) report as the critical toxicity study. He noted that the European Union and Health Canada had concluded that the developmental neurotoxicity studies of Hass and associates (Hass and Jakobsen, 1993; Hass et al., 1995, 1997) were more appropriate critical studies for xylene toxicity. Other panelists noted that toxicity studies evaluating different endpoints (Condie et al., 1988; Molnár et al., 1986) had found no difference in potency among the three isomers.

The panel discussed the sponsors’ presentation of the Hazard Quotient (HQ) on p. 150 of the document, together with the Adjustment Factors in Table 8.2. One member thought the document needed to be strengthened by further discussing the uncertainty factors included in each of the two factors comprising the HQ: the numerator (Exposure) and the denominator (Health Benchmark). Another member said he considered the database from which the HQ was derived to be inadequate because it contained no data on children or relevant data on young animals. Since nothing was known about the pharmacokinetics, metabolism, or sensitivity of children, it was indefensible to reduce the database uncertainty factor from 3 to 1. Several other panelists also said they were not convinced that this uncertainty factor should be reduced to from 3 to 1.

One member said the document apparently did not consider that CYP2E1 enzyme activity varies over seven-fold between newborns and adults. The presenter responded that modeling work had been conducted that addressed this CYP2E1 variation (Pelekis et al., 2001), and the investigators had concluded that children and adults would have similar xylene blood levels based on hepatic metabolism. Another member replied that the work of these investigators was not sufficient, because pulmonary metabolism also needs to be addressed.
7.2.2 Risk Characterization Methodology

Several panelists thought that using the Hazard Quotient (HQ) approach was appropriate for the xylenes. They said HQ values <1 indicate no hazard, as long as the context of the numerator (Exposure) and the denominator (Health Effects) are the same for the HQ. One member added that interpreting HQ values >1 can be challenging, and that HQ values >10 usually are considered to indicate problems. Another member said that adding HQs from different exposures to obtain a Hazard Index (HI) as described on pp. 150-151 of the document was appropriate.

Another panelist noted that the HQ for chronic exposures appeared correct, but using this same approach for repeated acute exposures, such as listed in Table 8.6, might not be valid. The values in Table 8.6 could result in a HQ >1 if somewhat different exposure assumptions were used. He said more explanation was needed about the way the Acute Exposure Guideline Levels (AEGL 1, 2 and 3) were used to calculate the HQ. In addition, a panel member noted that it is difficult to know if the endpoint selected for chronic effects from animal studies is correct because of insufficient pharmacokinetic data to compare rodents and children.

7.2.3 Risk Characterization for Populations

Most panel members said the risks were adequately characterized for prospective parents and for the embryo and fetus, but not for nursing infants less than one year of age or for post-nursing infants through adolescence. Several panelists thought the children’s age group from birth to one year of age needed to be subdivided into separate populations. Others thought more information was needed on direct exposures of xylenes to infants and children (or to young laboratory animals) and also about the xylenes pharmacokinetics (absorption, distribution, metabolism, excretion) and pharmacodynamics in these human (or young laboratory animal) populations.

Two panelists suggested the scope of the risk characterization be expanded by adding more discussion of reasonably foreseeable use (beyond uses covered by the product label instructions) and misuse situations, especially those involving children’s use of consumer products and unique occupation exposures such as occur with technicians using xylenes in histopathology work. Other panel members disagreed that an expanded scope for the risk characterization was necessary.

8. Data Needs

8.1 Sponsor Presentation

Dr. Mark Saperstein of the BP Product Stewardship Group provided a brief overview of the sponsor’s conclusions with regard to data needs for xylenes under the VCCEP program (no presentation slides were used). Regarding hazard, he noted that Table 6.1 in the submission (pp. 37-38) lists the hazard endpoints that have been addressed for VCCEP Tiers 1, 2, and 3, together with the specific studies conducted and their results. Dr. Saperstein stated that all Tier 1 endpoints have been met. In addition, toxicity data on the xylenes or on similar aromatic
hydrocarbons are available to address the Tier 2 and 3 endpoints. Although the available reproductive toxicity study is a one-generation study, rather than the two-generation specified for VCCEP, the results of this study, taken together with two-generation studies on similar aromatic hydrocarbons, indicate reproductive toxicity is likely to be a less sensitive endpoint for xylenes than neurotoxicity. Similarly, since developmental and adult neurotoxicity studies have been conducted on xylenes and NOAELS and LOAELS had been identified, it did not appear that additional studies in this area would significantly improve the risk assessment for xylenes. He recommended no further toxicity testing of xylenes under the VCCEP framework. Dr. Saperstein concluded that the available studies address the endpoints of interest in the VCCEP Program and that additional data from toxicology tests outline in the VCCEP framework would not add appreciable information to improve the risk assessment for xylenes.

8.1.1 Clarifying Questions from the Panel

None.

8.2 Panel Discussion of Data Needs

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

10. **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.**

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

In these discussions, the individual panelists identified items they each considered to be data gaps or data needs. The entire panel then discussed the data gaps and needs. Following these discussions, individual panel members were free to modify or change their data gaps and needs. The final listing of data needs and gaps is as follows:

Data needs:

- Obtain additional ADME and pharmacokinetic information from newborn and young animals and, if feasible, also from children. (Some other panelists listed this item as a data gap. One member wanted this work to include determining the accumulation and the partition coefficients at air:blood and blood:tissue

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3 In the context of the VCCEP pilot program, *data gaps* are defined as areas that could benefit from additional data, additional analyses, or clearer presentation.

4 In the context of the VCCEP pilot program, *data needs* are defined as data gaps requiring additional work before the potential risk to children can be adequately characterized.
interfaces, identifying metabolites in specific organs, determining if the parent chemical is toxic, and identifying the mode of action.

- Divide the children’s birth-to-one-year age group into separate groups and conduct separate assessments on each subdivision.

Items listed by one or two panelists:
- Conduct a rat inhalation study from pre-weaning through maturation to obtain toxicity information resulting from direct exposure to xylenes during this time frame.
- Conduct a neurotoxicity study with dosing beginning at or before birth.
- Review the existing teratology studies to determine whether teratology existed at levels below those which produced maternal toxicity.
- Confirm the critical toxic effect directly in young animals, rather than extrapolating it from adults (one panelist listed this as a data gap).
- Determine whether critical functional effects, such as from the rotorod studies, are reversible.
- Expand the exposure analyses by moving beyond consideration of typical and high end levels to include probabilistic assessments and misuse scenarios.
- Explore the impact of using different assumption in the exposure assessment for parameters such as room size, air changes, frequency/duration of product use by child hobbyists, etc.
- Model inhalation exposure in infants and model episodic exposures from consumer products and for hobbyists.
- Calculate the levels of xylenes in breast milk.
- Replace the default uncertainty factors (UF) employed in the risk characterization with data-derived values from animal studies conducted at doses close to the estimated toxicity thresholds.
- Provide more hazard, exposure, and risk characterization information on the xylenes mixtures (several panelists listed this as a data gap).
- Develop a systematic approach for introducing uncertainty factors into the exposure estimates.
- One panelist presented the following statement as a data need for risk characterization: Comparison of the chronic RfD with a child’s exposure can sometimes be overly conservative. Therefore, the following procedure is recommended, each step of which more realistically estimates the risk to children. First, recalculate the health benchmark with the existing PBPK model using a UF of 10 for the intraspecies extrapolation and a UF of 3 for the database incompleteness and other factors as already established. Use the resulting RfD in the HI determination. If the HI exceeds 1, drop the subchronic-to-chronic uncertainty factor (UFs) from the analysis. The resulting RfD more closely matches what might be true in humans from shorter-term exposures. Reassess whether the HI is still exceeded. If it is, consider estimating a short-term risk value to match the shorter-term exposure to children. This last step most realistically estimates the likely risk to children. However, it is the most time-intensive of the steps and does not need to be invoked unless the prior two (more conservative) approaches yield an HI in excess of 1.
Data gaps:

Item listed by several panel members:
- Determine pulmonary metabolism and compare it to hepatic metabolism.

Items listed by one or two panelists:
- Present PBPK information from oral and dermal, as well as from the inhalation, perspective and explore genetic variability in the population and age-dependent variation among children to determine their enzyme variation.
- Determine effects of xylenes on pregnancy and on parturition in humans.
- Obtain and evaluate pediatric data on toxicity and ADME from poison control centers and hospitals treating accidental or intentional excessive exposures.
- Review post-mortem brain findings in solvent abusers, assessing demyelination of neurofibers and cellular atrophy.
- For the exposure assessment, expand the range of consumer products to include more products used by children or hobbyists, and investigate inhalation exposures occurring in schools located in different geographies.
- Explore the impact of using different assumptions in the exposure assessment for parameters such as room size, air changes, frequency and duration of product use by child hobbyists, etc.
- Explore how different activities occurring during pregnancy alter exposures (painting the nursery, etc.).
- Determine the impact of xylenes groundwater plumes on indoor air and home water supplies.
- Determine how xylenes get into foods, including the transport mechanism and fate.
- Explore feasibility of conducting a probabilistic exposure assessment.
- Determine whether the Life-Line CSF II exposure model adequately covers neonates.

9. References


Voluntary Children's Chemical Evaluation Program (VCCEP)
Peer Consultation Report on Xylenes

