Appendix A

Voluntary Children's Chemical Evaluation Program (VCCEP)
Peer Consultations on Benzene
June 15-16, 2006

List of Attendees

Appendix A

List of Attendees

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Appendix B

Voluntary Children's Chemical Evaluation Program (VCCEP)
Peer Consultations on Benzene
June 15-16, 2006

Meeting Materials

Agenda, Overview, Panel Charge, Panelist Biographical Sketches and Conflict of Interest/Bias Disclosures, and Presenter Biographical Sketches

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Agenda

VCCEP Peer Consultation for Benzene
Northern Kentucky University, METS Center
June 15-16, 2006

Thursday, June 15, 2006

8:00 Registration and Check In

8:30 Meeting Convenes*

Welcome: Ms. Jacqueline Patterson, *TERA*
Introductions and Disclosures, Panel
Meeting Process: Dr. Michael Dourson, Panel Chair

9:00 Sponsor Introduction

Presenter: Mr. Andrew Jaques, ACC Benzene, Toluene, and Xylenes VCCEP Consortium Manager

Sponsor Presentation on Hazard Assessment
Presenters: Human Health – Dr. David Pyatt, Summit Toxicology
Animal Toxicity – Dr. Ceinwen Schreiner, C&C Consulting
Clarifying Questions from Panel

Public Comments on Hazard Assessment
Clarifying Questions from Panel and Sponsors

Panel Discussion
Discussion of Panel Charge Questions Regarding Hazard Assessment

12:15 Lunch

1:15 Sponsor Presentation on Exposure Assessment
Presenter: Ms. Julie Panko, ChemRisk
Clarifying Questions from Panel

Public Comments on Exposure Assessment
Clarifying Questions from Panel and Sponsors

Panel Discussion on Exposure Assessment
Discussion of Panel Charge Questions Regarding Exposure Assessment

5:00 Adjourn

* Chair will call mid morning and mid afternoon breaks at convenient times

Friday, June 16, 2006

8:00 Registration

8:30 Meeting Re-convenes*

Sponsor Presentation on Risk Characterization
Presenter: Mr. Sean Hays, Summit Toxicology
Clarifying Questions from Panel

Public Comments on Risk Characterization
Clarifying Questions from Panel and Sponsors

Panel Discussion on Risk Characterization
Discussion of Panel Charge Questions Regarding Risk Characterization

12:15 Lunch

1:15 Sponsor Presentation on Data Needs
Presenter: Mr. Andrew Jaques, ACC Benzene, Toluene, and Xylenes VCCEP Consortium Manager
Clarifying Questions from Panel

Public Comments on Data Needs
Clarifying Questions from Panel and Sponsors

Panel Discussion on Data Needs
Discussion of Panel Charge Questions Regarding Data Needs

4:30 Closing Remarks and Evaluation of Meeting

5:00 Adjourn

* Chair will call mid morning and mid afternoon breaks at convenient times

Overview of the Peer Consultation Process

Introduction

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 consultation meetings for private and public sponsors since 1996 (see http://www.tera.org/peer for information about the program and reports from meetings). As a part of this program, *TERA* is organizing peer consultation panel meetings for assessments developed under the Voluntary Children's Chemical Evaluation Program (VCCEP). This panel meeting will review the assessment on Benzene, which was submitted by the American Chemistry Council (ACC) Benzene, Toluene, and Xylenes Consortium.

The VCCEP program is a voluntary pilot program and part of the Environmental Protection Agency's (EPA) Chemical Right-to-Know Initiative. The goal of EPA's VCCEP program is to enable the public to better understand the potential health risk to children associated with certain chemical exposures. EPA has asked companies which manufacture and/or import 23 chemicals (that have been found in human tissues and the environment in various monitoring programs) to volunteer to sponsor their evaluation in Tier 1 of a pilot of the VCCEP. Sponsorship requires the companies to collect or develop health effects and exposure information on their chemical(s) and then to integrate that information in a risk assessment and a "data needs" assessment. More information about the VCCEP is available in the December 26, 2000 Federal Register (65 FR 81700) (http://www.epa.gov/fedrgstr/EPA-TOX/2000/December/Day-26/t32767.htm) and on EPA's VCCEP web site (http://www.epa.gov/chemrtk/vccep/index.htm).

The purpose of this meeting is to provide a science-based peer consultation on the data needs for Benzene. The assessment developed by the sponsor is being considered by a panel of scientific experts using a peer consultation process developed by *TERA*. These experts have experience in toxicity testing, exposure evaluation, risk assessment, and children's health. *TERA* has selected Peer Consultation Panel members after careful consideration of nominations from the public, and is responsible for convening and chairing panel meetings to discuss the sponsors' submissions. *TERA* will prepare a report for the meeting and make this available to the public at http://www.tera.org/peer/VCCEP/benzene/benzeneWelcome.html. The peer consultation meeting is open to the public.

Background on the Voluntary Children's Chemical Evaluation Program (VCCEP)

The ACC Benzene, Toluene, and Xylenes Consortium has volunteered to sponsor a Tier 1 assessment for Benzene, including hazard, exposure, risk characterization, and data needs assessments, utilizing available data. The key question of the program and the peer consultation is whether the potential hazards, exposures, and risks to children have been adequately characterized and if not, what additional information is necessary.

The program was set up to use a tiered testing approach, which is explained in the December 26, 2000 Federal Register notice (http://www.epa.gov/fedrgstr/EPA-TOX/2000/December/Day-26/t32767.htm). For toxicity data, specific types of studies have been put into three tiers. For

exposure data, the depth of exposure information increases with each tier, with Tier 1 a screening level assessment and Tiers 2 and 3 more advanced assessments using exposure studies, monitoring data, and modeling. The Federal Register notes that the Tier 1 assessment should use all available data, and therefore some of the chemical assessment documents will include more than what is in the Tier 1 level.

The peer consultation is designed to be a forum for scientists and experts to exchange scientific views on the need for additional toxicity and exposure data and analysis. In selecting the panel, *TERA* has sought to involve stakeholders by considering their nominations for panel members, and has sought to have a range of perspectives on the panel. This is not a consensus based approach; rather the individual panel members will discuss their own views. In the meeting report, opinions of the individual panel members will be noted, along with areas of agreement and disagreement.

The VCCEP program is a voluntary program. The sponsor has volunteered to prepare the Tier 1 assessment. If data needs are identified through this process, the sponsor will choose whether or not to volunteer for Tier 2.

Benzene Peer Consultation Panel

A core group of panel members participates in all panel meetings to ensure consistency among the reviews. *TERA* received 50 nominations for core panel members in early 2002 from VCCEP stakeholders and other interested parties. After a thorough review of these nominees, as well as other scientists whom *TERA* independently identified, *TERA* selected a group of 9 scientists to be VCCEP core group members. Core members are invited to return on a year-by-year basis. The 2006 core group consists of 8 scientists, 4 of whom belonged to the original core group.

Additional *ad hoc* experts are invited by *TERA* to participate in panel meetings on a case-by-case basis to provide additional expertise relevant to a specific chemical or issue. Nominations for *ad hoc* panelists are solicited from interested parties or independently selected by *TERA*. *Ad hoc* panelists have the same status and responsibilities as the core group members.

The VCCEP Peer Consultation Panel for Benzene consists of 13 members: 5 from the core group plus 8 additional *ad hoc* members specifically selected for this meeting. The Panel includes scientific experts in toxicity testing, risk assessment, exposure assessment, and children's health, as well as a pediatrician. Collectively, this panel has many publications and presentations on topics related to children's health risk.

Each panel member has disclosed information regarding potential conflicts of interest and biases related to the VCCEP program, the sponsor, and Benzene. *TERA* evaluated these disclosures when selecting panel members. Short biographical sketches and disclosure statements for panel members are provided in this package.

Conduct of the Peer Consultation Meeting

TERA developed a "charge" document that identifies the scientific issues to be discussed by the panel. The panel received a copy of the sponsor's submission, the charge, and key references approximately six weeks prior to the meeting to ensure adequate time to carefully review the document and prepare for the meeting discussions.

The meeting will be organized to make the best use of the time available to hear and discuss the opinions of the panelists regarding the charge questions and the data needs. The meeting will begin with panel introductions and a discussion of conflict of interest and bias issues. The discussion will then address the four assessment sections of the sponsor's submission (hazard, exposure, risk characterization, and data needs). To start each discussion section, the authors of the assessment document will make short presentations. These presentations will highlight the salient points and issues. Panelist will have the opportunity to ask clarifying questions of the authors.

Public Observation and Comments

Members of the public have been invited to attend this VCCEP Peer Consultation Meeting to observe the Panel discussions. This meeting also is being broadcast via a web cast. Meeting attendees and web cast participants were requested to register in advance for the meeting. The public also was invited to prepare brief technical comments on the assessment document and to submit their written comments prior to the meeting. Several public comments have been received. Meeting observers also will be permitted to make brief technical comments at the meeting, as time permits. Panel members and sponsors may ask clarifying questions of those making comments.

Meeting Report

TERA will prepare a meeting report summarizing the sponsor presentations, the opinions and recommendations expressed by the panel members, and the data gaps and data needs identified by individual panelists. Written and oral comments from the public also will be included in the report. The meeting report will be a summary, rather than a transcript. The report will be reviewed by the panel for accuracy before it is finalized. Sponsors and observers presenting oral comments will be offered the opportunity to review the summaries of their presentations. The finalized report will then be made available to the public at http://www.tera.org/peer/VCCEP/benzene/benzeneWelcome.html.

VCCEP Peer Consultation Panel Charge for Benzene

Introduction

The primary objective of this Peer Consultation Panel is to discuss whether the potential hazards, exposures, and risks for children have been adequately characterized for benzene, based on the information contained in assessment documents submitted by the sponsors and on other available information. If the potential hazards, exposures, and risks cannot be adequately characterized, then data needs should be identified. The panel's job is not to critique the assessment document *per se;* rather, the panelists use the document and its references as a source of information. The panel is not required to reach consensus positions on any issues or conclusions. Panelists who believe a chemical has not been adequately characterized will be asked to identify what additional information is needed and why they believe it is necessary. All the panelists will be encouraged to discuss and debate each other's suggestions and comments, providing scientific rationales for their points of view. *TERA* will compile the panel discussions in a meeting report that will be sent to the sponsor and made available to the public.

TERA has prepared this charge to help the panel discuss the sponsor's submission and address whether a chemical has been adequately characterized. The topics are consistent with the directions for VCCEP submissions given in the December 26, 2000, Federal Register: http://www.epa.gov/fedrgstr/EPA-TOX/2000/December/Day-26/t32767.htm.

Panelists should keep in mind the following directives from the Federal Register regarding any recommendations for additional testing: (1) if specific toxicity studies are indicated, they should be chosen from the next tier of studies within the overall framework. They should allow flexibility to pursue either additional toxicity testing and/or exposure evaluation, allowing sponsors to select the option which will most quickly, directly, and cost-effectively reduce uncertainty and allow the creation of a risk assessment; (2) EPA is committed to avoiding duplicative testing, and to reducing, refining, and replacing animal testing when valid alternatives exist; (3) if relevant alternative test methods become validated, EPA will consider their immediate implementation in the program; (4) EPA encourages sponsors to combine tests where possible to conserve resources and reduce the number of animals required for testing; and (5) the Tier 2 and Tier 3 testing will be limited to chemicals for which there is a clear need.

Hazard Assessment

1. Discuss whether the available information 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?

Exposure Assessment

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.

Risk Characterization

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

    10a. 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?

10b. 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?

Data Needs

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*.

[*] 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.

[†] 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. Not all data gaps will be considered data needs. The panelists may consider the risk characterization results when determining whether a data gap is a data need.

Conflict of Interest and Panel Biographical Sketches

Following NAS guidance, *TERA* creates panels that have a balance of scientific viewpoints on the issues to be discussed. As a result, *TERA*'s panels have a broad and diverse range of knowledge, experience, and perspective, including diversity of scientific expertise and opinion. In addition, *TERA* creates panels with multiple organizational perspectives (e.g., academic, consulting, environmental, government, and industrial/commercial). However, 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.

TERA is conducting this VCCEP Benzene Peer Consultation under its Peer Consultation Program. This program is principally funded by a Cooperative Agreement with the U.S. EPA, the purpose of which is to design, develop, and manage a Peer Consultation process that will serve as a public scientific forum. *TERA's* role in managing the peer consultation is undertaken primarily at the request of and for the benefit of non-federal stakeholders, particularly the sponsors of VCCEP chemicals.

TERA has performed work for organizations associated with VCCEP, both in the past and at the present time. These include the U.S. EPA, the American Chemistry Council, and some companies that are sponsors of VCCEP chemicals. *TERA* has conducted assessments and analysis for a number of chemicals included in the VCCEP pilot program in the past (i.e., acetone, decabromodiphenyl ether, methyl ethyl ketone, toluene, and xylenes) and currently is doing work on trichloroethylene. This work has been done for a variety of public and private sponsors, but none of it is directly related to the VCCEP assessments.

The purpose of this VCCEP Benzene Peer Consultation is to gather the scientific opinions of a range of experts with relevant knowledge and experience, including those who may be affiliated with organizations or companies with an interest in the outcome. All panelists were selected by *TERA* based upon their expertise and qualifications. They are employed by many types of organizations. *TERA* strived to create a balance of expertise and affiliations for this consultation meeting; however, *individual panel members represent their own expertise and views*, not those of their employer, of any group who may have nominated them, or any group with whom they may be associated. This panel is a distinguished group with many years experience in a wide range of disciplines.

An essential part of panel selection is the identification and disclosure of conflicts of interest and biases. Prior to selecting the core and *ad hoc* panelists, *TERA* requested each panel member to complete a questionnaire to determine whether their activities, financial holdings, or affiliations could pose a real or perceived conflict of interest or bias. The completed questionnaires were reviewed by *TERA* staff and discussed further with panel candidates as needed. (See http://www.tera.org/peer/COI.html for *TERA's* conflict of interest and bias policy and procedures for panelist selection).

TERA has determined, and each panel member has certified, that he or she has no conflicts of interest and is able to objectively participate in this peer consultation.

A brief biographical sketch of each panel member is provided below, together with a disclosure statement describing any potential conflict of interest or bias issues. The disclosures are specific

to benzene and the benzene sponsors. Brief biographical sketches of the sponsors' presenters follow the biographical sketches of the panel members.

Dr. John Christopher

Dr. Christopher is a staff toxicologist with the Department of Toxic Substances Control, California Environmental Protection Agency. In this position he reviews, critiques, and approves assessments of risk to human health and ecological risk assessments at military facilities and other hazardous waste sites and permitted facilities in California. He constructs multi-pathway risk assessments to identify numerical criteria for classifying hazardous levels of metals and organic chemicals in waste. He also uses Monte Carlo methods in various exposure settings to identify levels protective of human health. He has received Certificates of Recognition for contributions resulting in the successful transfer of a hazardous waste landfill at a former naval shipyard in Vallejo, CA, for a prescribed burn to uncover unexploded ordnance at a former fort in, Monterey, CA, and also for cleanup of a fleet industrial supply center in Alameda, CA. In addition, he has received a Sustained Superior Accomplishment Award from California Department of Toxic Substances Control for risk assessment of metals in hazardous waste.

Prior to his current position with the State of California, Dr. Christopher conducted risk assessments for ICF Kaiser Engineers and IT Corporation. He also worked for research laboratories where he conducted and managed animal studies.

Dr. Christopher earned a B.S in Biology from Georgetown University, Washington DC, and a M.A. in Pharmacology from Stanford University, Palo Alto, CA. He received his Ph.D. in Biological Science from Oregon State University, Corvallis OR.

Dr. Christopher is a Diplomate of the American Board of Toxicology and a former member of this Board. He has served as President and held several other offices in the Risk Assessment Specialty Section of the Society of Toxicology and also in SOT's Northern California Chapter. He is a peer reviewer for *Toxicological Sciences, Risk Analysis*, *Human and Ecological Risk Assessment,* and *CRC Critical Reviews in Toxicology.*

DISCLOSURE: Dr. Christopher's current responsibilities from the California EPA include evaluating exposures from hazardous waste sites that may contain benzene. In 2002, Dr. Christopher performed non-VCCEP-related consulting services for the American Chemistry Council (ACC) and received payment for his services. Dr. Christopher requested inclusion of the following statement: "Dr. Christopher performs scientific peer consultation for *TERA* as a private individual. His employer, the California Department of Toxic Substances Control, is not bound in any way by the opinions he expresses or by consensus agreements to which he chooses to be a party."

TERA has determined that Dr Christopher has no conflicts of interest that would disqualify him for panel membership. His current responsibilities at the California EPA and his consulting work in 2002 for ACC are being disclosed to assure transparency. *TERA* does not believe these activities will impair Dr. Christopher's scientific objectivity as a VCCEP benzene panel member.

Dr. John DeSesso

Dr. John DeSesso is a charter member of the technical staff of Mitretek Systems, an independent, not-for-profit company that was formed from several parts of The MITRE Corporation. Dr. DeSesso is a Senior Fellow and the Director of the Biomedical Research Institute at Mitretek Systems. Dr. DeSesso has extensive experience in reproductive and developmental toxicity, risk assessment, ecological risk assessment, and the use of bioavailability in risk assessments.

Dr. DeSesso received his Ph.D. in Anatomy and Teratology from the Medical College of Virginia at Virginia Commonwealth University. He is a Diplomate of the American Board of Forensic Examiners and the American Board of Forensic Medicine, specializing in anatomy and risk assessment, and a Fellow of the Academy of Toxicological Sciences. Prior to joining Mitretek Systems, Dr. DeSesso was a Senior Principal Scientist at MITRE Corporation where he evaluated chronic studies (with special attention to reproductive toxicity and teratology) for EPA's Office of Pesticides, conducted biostatistical analyses of data and risk assessment techniques, predicted toxic effects based upon structure-activity relationships for new chemicals, provided quality assurance of risk assessments performed by contractors for the U.S. Air Force, and performed independent research into the mechanisms that underlie chemically induced birth defects. Dr. DeSesso's research focus has been the elucidation of the mechanisms underlying teratogenesis and designing strategies to ameliorate the untoward effects.

Dr. DeSesso is currently a faculty member at Georgetown University School of Medicine, Rosalind Franklin University of Medicine and Science, San Diego State University/Graduate School of Public Health, and the University of North Texas Health Sciences Center. He is an active member of numerous scientific societies where he has held various office positions including but not limited to: Academy of Toxicological Sciences, American College of Toxicology, American Society for Reproductive Medicine, Society for Risk Analysis, Society of Toxicology, and Teratology Society.

Dr. DeSesso has been an active member of the peer-review process reviewing manuscripts for major journals and grant proposals on a national and international level (e.g., U.S. EPA, United States-Israel Binational Science Foundation, NIH, NIEHS). He has been invited frequently to serve as the Chairman of scientific sessions at national and international scientific meetings, especially those involving mechanisms or amelioration of developmental toxicity and ecological risk assessment. He has served as an invited faculty member or invited participant on many panels, refresher courses, and working groups that have been sponsored by a variety of federal agencies (e.g., USEPA, FDA, NIEHS) and professional societies (e.g., Teratology Society, Toxicology Forum, American College of Veterinary Pathologists, Society of Environmental Toxicology and Chemistry, American College of Toxicology). Also, Dr. DeSesso is published extensively in the above areas of expertise, with publications both public and private numbering well over 100.

DISCLOSURE: As an employee of Mitretek Systems, Dr. DeSesso participated in a laboratory site visit at the ExxonMobil Biomedical Sciences Institute facilities in 2003 and analyzed animal toxicity data for Chevron Corporation on non-benzene chemicals in 2001. Mitretek Systems received payment for these services.

TERA has determined that Dr. DeSesso has no conflicts of interest that would disqualify him for panel membership. His activities with ExxonMobil Biomedical Sciences and with Chevron in 2001 and 2003 are being disclosed to assure transparency. *TERA* does not believe these activities will impair Dr. DeSesso's scientific objectivity as a VCCEP benzene panel member.

Dr. Michael Dourson

Dr. Michael Dourson directs Toxicology Excellence for Risk Assessment (*TERA*), a nonprofit corporation dedicated to the best use of toxicity data for estimating risk assessment values. *TERA*'s projects include the development of complex risk assessments, such as soluble nickel salts; research into improvements of risk methods, such as differential sensitivity of children and adults to chemical toxicity, organizing peer review and consultation meetings for risk assessment topics and documents; and education and outreach on risk assessment values through lectures and data bases, including the International Toxicity Estimates for Risk (*ITER*).

Before founding *TERA* in 1996, Dr. Dourson held leadership roles in the U.S. Environmental Protection Agency for fifteen years; as chair of EPA's Reference Dose (RfD) Work Group, charter member of the EPA's Risk Assessment Forum and chief of the group that helped create the Integrated Risk Information System (IRIS) in 1986. Dr. Dourson received his Ph.D. in Toxicology from the University of Cincinnati and a B.A. in biology from Wittenberg University. Dr. Dourson's research interests include investigating methods to extrapolate toxicity data garnered on experimental animals or healthy adults to the appropriate sensitive human population. Topics such as adversity of effect and characterization of risk are also of interest.

Dr. Dourson has served on numerous expert panels, such as EPA's peer review panels for IRIS assessments and its Risk Assessment Forum, *TERA*'s International Toxicity Estimates for Risk (*ITER*) independent peer reviews and consultations, FDA's Science Board Subcommittee on Toxicology, the NSF's Health Advisory Board, and SOT's harmonization of cancer and non-cancer risk assessment. Dr. Dourson has also organized over 16 symposia for 9 different organizations on a variety of topics, including: risk communication; chromium; information resources for toxicology and environmental health; risk assessment of essential trace elements; risk characterization; EPA's IRIS; uncertainty in risk assessment techniques; statistical and dose response models in risk assessment; workshop on benchmark dose methodology; basics of risk assessment; improvements in quantitative noncancer risk assessment; and neurotoxicity risk assessment.

Dr. Dourson is a Diplomate of the American Board of Toxicology and served on its Board as President, Vice President, and Treasurer. He is currently Secretary for the Society for Risk Analysis, and has also served as president of the Dose-Response Specialty Group of the Society for Risk Analysis, of the Society of Toxicology's Specialty Section on Risk Assessment and of the Ohio Chapter of the Society for Risk Analysis. He is currently on the editorial board of three journals. Dr Dourson has published more than 100 papers on risk assessment methods, has co-authored over 100 government risk assessment documents, and has made over 90 invited presentations.

DISCLOSURE: Dr. Dourson is Director of *TERA*. He has chaired or participated in over 100 scientific peer review meetings funded by numerous organizations including the American Chemistry Council (ACC) or by numerous companies, including several of the VCCEP benzene sponsors. To the best of his knowledge, none of these meetings have been specific to benzene. As an employee of *TERA*, Dr. Dourson recently assessed the toxicology and risk of chorpyrifos; Dow AgroSciences LLC provided some of the funding for this work. In 2003, he reviewed the U.S. EPA Office of Research and Development's Air Toxics Research Plan and Multiple Year Strategy documents, which included benzene. As an employee of *TERA*, Dr. Dourson also has contributed to non-benzene related research and development activities sponsored by ACC, DuPont, and BP; as well as contributed to some *TERA* projects that involved benzene in some fashion (See *TERA* disclosure above).

TERA has determined that Dr Dourson has no conflicts of interest that would disqualify him for panel membership. His previous activities with ACC and company sponsors (and *TERA*'s previous work for the company sponsors) are being disclosed to assure transparency. *TERA* does not believe these activities will impair Dr. Dourson's scientific objectivity as a VCCEP benzene panel member.

Dr. Jeffrey Fisher

Dr. Fisher is a Professor and Department Head of the Department of Environmental Health Science, College of Public Health at the University of Georgia. He also serves as Director of the Interdisciplinary Toxicology Program. Dr Fisher's research interests are in the development and application of biologically based mathematical models to ascertain health risks from environmental and occupational chemical exposures. Dr Fisher's modeling experience includes working with chlorinated and non-chlorinated solvents, fuels, PCBs and perchlorate. He has developed PBPK models for use in cancer risk assessment, estimating lactational transfer of solvents, understanding *in utero* and neonatal dosimetry, quantifying metabolism of solvent mixtures and developing biologically motivated models for the Hypothalamic-Pituitary-Thyroid axis in rodents and humans. Dr. Fisher has 20 years of experience in physiological modeling and has trained graduate students and postdoctoral fellows on the concepts and application of physiological models.

Dr. Fisher has a B.S. degree in biology from the University of Nebraska at Kearney, a M.S. degree in biology/ecology from Wright State University, and a Ph.D. in Zoology/Toxicology from Miami University. He spent most of his career at the Toxicology Laboratory, Wright Patterson AFB, where he was Principal Investigator and Senior Scientist in the Toxics Hazards Division and Technical Advisor for the Operational Toxicology Branch. He was a Visiting Scientist at the Chemical Industry Institute of Toxicology in 1996 and at the NIOSH Taft Laboratory in 1999. During this time, he also served as Adjunct Professor in the Department of Pharmacology and Toxicology at Wright State University. He accepted an academic position at the University of Georgia in July 2000.

Dr. Fisher has published over 90 papers on pharmacokinetics and PBPK modeling in laboratory animals and humans. He has served on several panels and advisory boards for the Department of Defense, the Agency for Toxic Substances and Disease Registry, the U.S. EPA, and for non-profit organizations. He also has been a U.S. delegate for the North Atlantic Treaty Organization.

Dr. Fisher also served on the International Life Sciences Institute Steering Committee, which evaluated chloroform and dichloroacetic acid using EPA-proposed Carcinogen Risk Guidelines. He is Past President of the Biological Modeling Specialty Section of the Society of Toxicology, reviewer for several toxicology journals, and was Co-Principal Investigator on a National Institutes of Health (NIH)-supported workshop on Mathematical Modeling at the University of Georgia in the fall of 2003. He is a member of the National Academy of Sciences subcommittee on Acute Exposure Guideline Levels (AEGLs) since 2004 and a Fellow of the Academy of Toxicological Sciences. He is on the editorial board for the International Journal of Toxicology and the Journal of Toxicology and Environmental Health.

DISCLOSURE: None

Dr. Michael Greenberg

Dr. Greenberg is Professor of Emergency Medicine and Professor of Public Health at the Drexel University College of Medicine (DUCOM) in Philadelphia and Clinical Professor of Emergency Medicine at Temple University School of Medicine. He is the Program Director for the Medical Toxicology Fellowship Training Program at DUCOM where he also serves as the Chief of the Division of Occupational and Environmental Emergency Medicine and the Associate Director of the Division of Medical Toxicology. Dr. Greenberg has served as an instructor in the Department of Defense Domestic Preparedness Program and as a consultant regarding chemical and biological weapons of mass destruction to the U.S. State Department's Bureau of Diplomatic Security and the U.S. Navy's Office of Homeland Defense. In addition, he has served as principle investigator for several research projects dealing with hospital preparedness against weapons that might be used by terrorists funded by the U.S. Army. His primary clinical practice involves medical, occupational, and environmental toxicology, and he serves as a clinical consultant for the Philadelphia Poison Control Center.

Dr. Greenberg holds current board certifications in three specialties: Medical Toxicology, Preventive Medicine (Occupational/Environmental Medicine), and Emergency Medicine. He is a Fellow of the American College of Preventive Medicine, the American Academy of Emergency Medicine, the American College of Occupational and Environmental Medicine, and the American College of Medical Toxicology.

Dr. Greenberg is the Editor-in-Chief of *Occupational, Industrial, and Environmental Toxicology*, as well as *Greenberg's Atlas of Emergency Medicine*. He is the author of over 250 scientific articles, abstracts, and book chapters. Dr. Greenberg has served on the American College of Medical Toxicology (ACMT) committee to examine the use of potassium iodide in radiological emergencies and he currently serves as the Chair of the Biomonitoring Committee for ACMT. He is an elected member of the Board of Trustees of the American Academy of Clinical Toxicology, and he is a charter member of the American Academy of Emergency Medicine. Dr. Greenberg served as a Medical Officer with the United States Marine Corps Reserve while serving in the United States Naval Reserve from 1985 to 1995, and he served on active duty during Operation Desert Storm.

DISCLOSURE: Dr. Greenberg is employed by the Drexel University College of Medicine and Temple University School of Medicine, and he is a Partner in Newfields Denver LLC, a consulting company. At the time this disclosure was written, he is not engaged in any consulting work on benzene or any work for the sponsoring companies; however, in the past Dr. Greenberg has served as an expert medical toxicologist in legal matters involving benzene on behalf of both plaintiffs and defendants. To the best of his knowledge and recollection, none of these benzene cases involved the VCCEP benzene sponsors. Dr. Greenberg believes that others working for his universities or for Newfields Denver LLC may provide or have provided consultative services to a number of companies in the petroleum and chemical sectors, including some of the VCCEP benzene sponsors; however, Dr. Greenberg is not specifically aware of any of these projects**.**

TERA has determined that Dr Greenberg has no conflicts of interest that would disqualify him for panel membership. His past activities as an expert witness, as well as the past and current activities of his university employers and of Newfields Denver LLC, are being disclosed to assure transparency. *TERA* does not believe these activities will impair Dr. Greenberg's scientific objectivity as a VCCEP benzene panel member.

Dr. Pertti (Bert) Hakkinen

Dr. Pertti (Bert) Hakkinen is on the staff of the European Commission at the EC's Joint Research Centre (JRC) in Ispra, Italy. He is in the JRC's Physical and Chemical Exposure Unit of the Institute for Health and Consumer Protection where he helps develop and manage work packages for EIS-ChemRisks, the European Information System on risks from chemicals released from consumer products and articles (textiles, toys, etc.).

Dr. Hakkinen is a member of the Scientific Advisory Panel of the (U.S.) Mickey Leland National Urban Air Toxics Research Center and has served as the vice chair of this panel since March 2003. Prior to joining the European Commission's staff, Dr. Hakkinen was on the staff of Toxicology Excellence for Risk Assessment (*TERA*). Before joining *TERA*, he worked at the Procter & Gamble Company to provide global human exposure and risk assessment support for numerous types of consumer products and chemicals. While at Procter & Gamble, he chaired the Exposure Assessment Task Group of the Chemical Manufacturers Association (now the American Chemistry Council) for several years, and was a chair of the American Chemistry Council's Human Exposure Assessment Technical Implementation Panel.

Dr. Hakkinen earned a B.A. in Biochemistry and Molecular Biology from the University of California, Santa Barbara, and received his Ph.D. in Comparative Pharmacology and Toxicology from the University of California, San Francisco. He served as a postdoctoral investigator in respiratory toxicology, and exposure and risk assessment at the Biology Division of the Oak Ridge National Laboratory. Dr. Hakkinen has been an invited expert or reviewer for the U.S. EPA, Health Canada, and other associations to develop or revise human exposure assessment guidance, resource documents, and software. He has lectured on exposure and risk assessment, risk perception, and risk communication at the University of Cincinnati and elsewhere.

Dr. Hakkinen is a member of the Society of Toxicology (SOT) and a charter member of the Society for Risk Analysis (SRA) and the International Society of Exposure Analysis (ISEA). He proposed the idea for the *Residential Exposure Assessment. A Sourcebook*, developed and published in 2001 via the expertise and involvement of members of SRA's Exposure Assessment Specialty Group, ISEA members, and many others. Dr. Hakkinen received SRA's Outstanding Service Award in 1996. He was on the editorial board of *Toxicology* and was a co-editor and co-author of the latest edition of *Information Resources in Toxicology* and is a co-editor and co-author of the new edition under development. Further, he is a co-editor and co-author of the upcoming new edition of the *Encyclopedia of Toxicology*. Dr. Hakkinen has authored and co-authored numerous other publications, including ones on consumer product exposure and risk assessments, consumer risk perceptions, toxicological interactions, respiratory tract toxicology, and computer software and databases.

DISCLOSURE: Dr. Hakkinen chaired Exposure Assessment Task Groups and Panels of the American Chemistry Council (ACC) in 2001 and earlier. Dr. Hakkinen requested inclusion of the following statement: "The views that Dr. Hakkinen expresses as a VCCEP panelist are his own and do not necessarily represent official views of the European Commission."

TERA has determined that Dr Hakkinen has no conflicts of interest that would disqualify him for panel membership. His chairing of ACC task groups and panels in 2001 and earlier is being disclosed to assure transparency. *TERA* does not believe this past activity with ACC will impair Dr. Hakkinen's scientific objectivity as a VCCEP benzene panel member

Dr. Sam Kacew

Dr. Sam Kacew is a Professor in the Department of Cellular and Molecular Medicine, Faculty of Medicine, as well as a scientist of the Institute of Population Health at the University of Ottawa. His responsibilities include teaching medical students and graduate students the techniques required to write and publish peer-review papers. His current research involves the effects of chemical contaminants in breast milk on infants, the role of confounding factors in toxicity testing, as well as the basis for differences in responsiveness to chemicals between infants and adults.

Dr. Kacew received his Ph.D. in Pharmacology from the University of Ottawa. He served as a Postdoctoral Fellow for the Medical Research Council of Canada at the University of Montreal. Dr. Kacew was certified in 1994 as a Fellow of Academy of Toxicological Sciences. He has received numerous awards, including several achievement, recognition, public communications, and travel awards from the Society of Toxicology (SOT), the United States-China Foundation, and the National Science Council of the Republic of China.

Dr. Kacew has served on numerous expert panels and committees, including membership on the National Advisory Committee on Environmental Contaminants and the Implications for Child Health and the National Academy of Sciences (U.S.) Committee on Toxicology, and Chair of the National Academy of Sciences Subcommittee on Iodotrifluoromethane. He also has served as a chairman for a variety of symposiums, panels, and committees including the SOT Annual Meeting's General Toxicology Session, the Federation of American Societies for Experimental Biology Annual Meeting, an Assessment Panel for the Canadian Council on Animal Care, a SOT Symposium on Use of Moderate Dietary Restriction in Safety Assessment, and a SOT Symposium on the Role of Diet and Obesity in Endocrine Disruption. He has presented hundreds of invited lectures for a variety of federal and state government agencies, colleges and universities, private companies, and international organizations. He was an invited participant to the American Society for Pharmacology and Experimental Therapeutics Meeting, the Federation of American Societies for Experimental Biology Annual Meeting, the International Life Sciences Institute, the Chalk River Nuclear Labs, Turkey Society of Biochemistry, Society of Toxicology of Taiwan, and the Korea Society of Toxicology.

Dr. Kacew is on a number of grant committees and has served as an external referee for grants and fellowships for a wide variety of organizations and government agencies. He is currently the Editor-in-Chief the *Journal of Toxicology and Environmental Health*, North American Editor of *Toxicology and Environmental Chemistry*, an Associate Editor for *Toxicology and Applied Pharmacology*, an assistant editor for TOMES (Micromedex, Inc.), Guest Editor for *Toxicology and Applied Pharmacology* special issue on Toxicological Reviews in Fetal Childhood Development, as well as a member of the editorial board of a number of other journals. Dr. Kacew has over 140 publications in peer-reviewed journals and books in the area of toxicology, risk assessment, and children's health. He has also served as an editor for a number of books on toxicology and children.

DISCLOSURE: None

Dr. Erica Liebelt

Dr. Erica Liebelt is an Associate Professor of Pediatrics and Emergency Medicine at the University of Alabama at Birmingham School of Medicine. She is also the Director of Medical Toxicology Services at the Children's Hospital and UAB Hospitals as well as Associate Medical Director of the Regional Poison Control Center/Birmingham. She graduated summa cum laude from Duke University and completed her medical degree at the University of Cincinnati Medical School with highest honors. Her postgraduate medical education includes a pediatric residency at Children's Hospital Medical Center in Cincinnati, where she also served as Chief Resident. Dr. Liebelt completed a pediatric emergency medicine fellowship at Children's Hospital in Boston and a medical toxicology and pharmacology fellowship at Harvard Medical School and the Massachusetts Poison Control Center in Boston.

Dr. Liebelt held academic appointments at Yale University and Johns Hopkins School of Medicine before moving to Birmingham where she developed medical toxicology services. She was also the director of the Yale-New Haven Hospital Children's Lead Program.

She has authored over 60 book chapters and manuscripts for leading toxicology textbooks and peer-reviewed journals. Dr. Liebelt is on the Executive Board of Directors of the American College of Medical Toxicology (ACMT). She also serves on the editorial board of the journal Clinical Toxicology and the Section Editor for Therapeutics and Toxicology in Current Opinion in Pediatrics. Dr. Liebelt currently is a member on the American Board of Pediatrics Certifying Examination Committee as well as the American Association of Poison Control's Specialist in Poison Information Certifying Committee. In the past, she was also a member of the Sub-board of Medical Toxicology with the American Board of Emergency Medicine for nine years.

Dr. Liebelt has lectured both nationally and internationally on various topics in medical toxicology. She has served on several expert panels for the Centers for Disease Control, the Agency for Toxic Substances and Disease Registry, and the National Toxicology Program of the NIH. Her research interests include antidepressant poisoning, pediatric environmental toxicology, and curriculum development in medical toxicology.

DISCLOSURE: None

Dr. David MacIntosh

Dr. MacIntosh is Principal Scientist at Environmental Health & Engineering Inc. where he leads exposure and risk assessment projects for commercial, government, and legal clients. In addition, he is an Adjunct Associate Professor of Environmental Studies at Brandeis University and Co-Director of a course on environmental sampling and analysis methods at the Harvard University School of Public Health. Dr. MacIntosh has extensive experience in the measurements and models of human exposure to hazardous substances through air, water, surfaces, and food. His major interests include air pollution, bioaerosols, pesticides, volatile organic compounds, heavy metals, aggregate and cumulative exposure assessment, longitudinal and chronic exposure, monitoring methods, and study design.

Dr. MacIntosh obtained his B.S. and M.S. degrees in Decision Science and Environmental Science from Indiana University and his Sc.D. in Environmental Health from the Harvard School of Public Health. Prior to joining EH&E, Dr. MacIntosh was a tenured faculty member in the Department of Environmental Health Science at the University of Georgia. He is a frequent author and speaker on scientific topics relating to human exposure to environmental contaminants. He also is a first draft author of a guidance manual on human exposure assessment published by the World Health Organization. He serves on the Science Advisory Panel to the U.S. Environmental Protection Agency for the Federal Insecticide, Fungicide, and Rodenticide Act and is an advisor to the WHO International Program on Chemical Safety.

DISCLOSURE: None

Dr. Thomas McDonald

Dr. Thomas McDonald currently is Principal Research Scientist in Pre-Clinical Development at Bayer HealthCare LLC. He previously was Manager of Toxicology for Arysta LifeScience North America. Where he coordinated all toxicological activities for the company's crop-protection products throughout North America. The position provided technical expertise and support to internal personnel on matters related to toxicology, oversaw toxicological testing and risk assessment activities in support of product registration, and provided regulatory support to the company's global business units.

Prior to his tenure at Arysta LifeScience, Dr. McDonald served for 10 years a Staff Toxicologist with the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. His primary activities included hazard identification and dose-response assessment of carcinogens, development of children's cancer guidelines, peer review, and technical support to the state's science advisory boards. Dr. McDonald served as technical lead to re-evaluation the health standards of benzene for California's drinking water and Proposition 65 programs. He also served as lead scientist to evaluate the potential susceptibility of children to benzene for California's Toxic Air Contaminant program.

Dr. McDonald received his Ph.D. in Environmental Health Sciences from the University of North Carolina, Chapel Hill, and holds degrees in molecular biology and public health from the University of California at Berkeley. His master's research involved biomonitoring of benzene, and his doctoral dissertation examined macromolecular adducts to study the disposition of reactive metabolites of benzene.

Dr. McDonald's professional activities include membership in scientific societies, serving recently as President of the Genetic and Environmental Toxicology Association, as well as mentoring graduate students. He has over 20 publications in peer-reviewed journals or proceedings, including 9 on benzene, two book chapters and numerous government documents as first author.

DISCLOSURE: Before becoming a toxicologist, Dr. McDonald started his career as a technician for Chevron Research Company in the products research lubricants division (1985-1988).

TERA has determined that Dr McDonald has no conflicts of interest that would disqualify him for panel membership. His 1985-1988 employment by the Chevron Research Company is being disclosed to assure transparency. *TERA* does not believe this past employment will impair Dr. McDonald's scientific objectivity as a VCCEP benzene panel member.

Ms. Ruthann Rudel

Ms. Ruthann Rudel is a Senior Scientist responsible for toxicology and environmental risk assessment for the Silent Spring Institute. She manages the toxicology and environmental exposure components of the multi-disciplinary Cape Cod Breast Cancer and Environment Study. For this study, Ms. Rudel designs and manages investigations of the hypothesis that exposure to endocrine disruptors might play a role in breast cancer etiology. Her work includes designing and managing field sampling programs and developing exposure variables, as well as managing work with study collaborators with at Tufts Medical School, Harvard University School of Public Health, and other institutions. She has considerable experience in risk assessment of environmental chemicals.

Prior to joining the Silent Spring Institute, Ms. Rudel worked as an environmental toxicologist for Gradient Corporation. As such, she evaluated the health effects of exposure to hazardous chemicals in the environment in order to provide a sound basis for environmental management decisions. She reviewed international properties contaminated with pesticides and chlorinated solvents, and evaluated blood biomarkers and exposure from inhalation, soil and dust ingestion and bioconcentration, and fish ingestion. In addition, Ms. Rudel also worked as an Editor for World Information Systems where she researched, wrote and edited a national weekly newsletter entitled, *Hazardous Materials Intelligence Report*.

Ms. Rudel received her M.S. in Hazardous Materials Management from Tufts University and has completed graduate coursework at the Harvard Extension School and the New England Epidemiology Institute. She also received a B.A. in Chemistry with High Honors in Neuroscience from Oberlin College.

Ms. Rudel's professional activities include membership in numerous scientific societies and participation as a reviewer for journals and on peer review panels. Ms. Rudel is a member of the Society of Toxicology, Society for Risk Analysis, and the International Society for Exposure Analysis. She is an *ad hoc* manuscript reviewer for four scientific journals on toxicology, environmental health, and environmental science. She has participated as a reviewer for various government, non-profit, and academic organizations. She also has numerous publications and presentations in the areas of exposure assessment, geographic information systems (GIS), and endocrine disruptors.

DISCLOSURE: None

Dr. Robert Snyder

Dr. Snyder is Associate Dean for Research and Professor of Toxicology and Pharmacology at the Ernest Mario School of Pharmacy of Rutgers, the State University of New Jersey. His other appointments include Adjunct Professor of Environmental and Community Medicine (Robert Wood Johnson Medical School of UMDNJ); Adjunct Professor of Pharmacology (Thomas Jefferson University, Philadelphia). He has served as Visiting Professor of Toxicology at the University of Tűbingen and at the GSF Forschungscentrum fűr Umwelt und Gesundheit Gmbh, Neuherberg, Germany. Previously he was Chairman of the Department of Pharmacology and Toxicology at the Ernest Mario School of Pharmacy; Director of the Graduate Program in Toxicology; Associate Director and later Director of the Environmental and Occupational Health Science Institute, a joint effort of Rutgers and UMDNJ.

Dr. Snyder received his Ph.D. in biochemistry from the State University of New York. For the past 40 years his research interest has been the mechanisms by which benzene causes bone marrow damage leading to aplastic anemia, myelodysplasia and leukemia. He participated in or organized international conferences on benzene in Washington (1970), Paris (1976), Research Triangle Park, NC (1988), Piscataway, NJ (1995), Ottawa, Canada (1998), Munich Germany (2000) and Washington, (2005). He was the principle organizer of the International Symposium on Biological Reactive Intermediates offered every five years from 1975 to the present. He has served as member and chair of the Toxicology Study Section (NIH), Health Effects Research Review Panel (USEPA), Committee on Toxicology (NAS/NRC, two terms), Chair of the NRC Committee on Alkybenzenes, Chair of the NRC Committee on Reference Doses for Chemical Warfare Agents, and served on NRC Committees on Spacecraft Maximal Allowable Concentrations, Permissible Exposure Levels for Military Jet Fuels, Alternative to Chlorofluorocarbons, Industrial Hygiene in the US Navy, and Risk Assessment for Flame Retardant Chemicals. He also served on the National Advisory Committee on Acute Exposure Guideline Level (USEPA) and has been appointed to the NRC Committee on the same subject. He also served on the FDA Committee on Impurities and is currently a member of the USEPA Science Advisory Board for Homeland Security. He has served as Board member and President of the American College of Toxicology and the Academy of Toxicological Sciences. He also is a member of the Society of Toxicology and the American Society for Pharmacology and Experimental Therapeutics.

DISCLOSURE: In 1977 and 1978 Dr. Snyder served as an expert witness on benzene for the American Iron and Steel Institute in OSHA hearings regarding occupational carcinogenesis. At times in the past his research has been funded by the National Institutes of Health, the Mobil Oil Company, and the American Petroleum Institute. He currently has research grant proposals pending with the American Petroleum Institute to study the impact of benzene metabolites on chromosome condensation and chromosome aberrations and also with a German insurance company to study the impact of inhaled benzene on human bone marrow implanted in immune deficient mice. Dr. Snyder has a consulting practice where he advises a wide diversity of clients; however, at the present time he is not a consultant for any of the VCCEP benzene sponsors.

TERA has determined that Dr Snyder has no conflicts of interest that would disqualify him for panel membership. His past activities as an expert witness in 1977 and 1978, the past and possible future funding of his research, and his consulting practice are being disclosed to assure transparency. *TERA* does not believe these activities will impair Dr. Snyder's scientific objectivity as a VCCEP benzene panel member.

Dr. Donna Vorhees

Donna J. Vorhees is a Principal Scientist with Menzie-Cura & Associates, Inc. where she directs human health risk assessment work and an instructor at the Boston University School of Public Health where she teaches a graduate-level course in risk assessment methods. Before joining Menzie-Cura & Associates, Inc., Dr. Vorhees completed a USEPA NNEMS Fellowship at EPA Region 1 in 1992-1993 researching indoor air quality. Dr. Vorhees serves as chair of the Exposure Assessment Specialty Group of the Society for Risk Analysis and is a member of the International Society of Exposure Analysis. She currently serves as a provisional member of the National Research Council Committee on Sediment Dredging at Superfund Megasites.

Dr. Vorhees earned her B.S. in biology from Bethany College in West Virginia and her master's degree and doctoral degree in Environmental Health from the Harvard School of Public Health.
She has extensive experience addressing environmental questions arising from multi-pathway human exposure to chemicals that have been released to indoor and outdoor environments at federal and state hazardous waste sites. Her research interests include development of probabilistic human exposure models; field surveys to collect data needed to support risk assessment; and preparation of environmental health educational materials. Dr. Vorhees conducted probabilistic analyses of multi-pathway exposure to PCBs in residences near the New Bedford Harbor, Massachusetts Superfund site, to chemicals that accumulate in fish from an offshore dredged material disposal site, and to persistent organochlorines that accumulate in agricultural products from the floodplain of a contaminated river.

Dr. Vorhees has considerable experience on projects involving the evaluation of indoor exposures to volatile organic compounds. For example, she co-authored guidance for the Maine Department of Environmental Protection for responding to petroleum releases inside residences, participated on the Massachusetts Department of Environmental Protection work group regarding its indoor air guidance, and managed numerous projects involving either indoor or subsurface sources of VOCs affecting indoor air quality. Dr. Vorhees also participated in activities of the TPH Criteria Working Group from 1997 to 2000, co-authoring the group's final report regarding risk-based remediation at petroleum release sites and serving as an instructor in several one-day workshops about fraction-based approaches to petroleum risk assessment. Dr. Vorhees participated in a consortium of industry, consulting, and Massachusetts government scientists to re-evaluate the Reference Dose for the aromatic fraction of JP-8 jet fuel.

DISCLOSURE: In 2001 Dr. Vorhees received funding from Chevron to participate in a consortium assessing the Reference Dose for jet fuel. In the past, her employer Menzie-Cura & Associates, Inc. (MCA) provided consulting services for some of the VCCEP benzene sponsors, and an MCA staff member currently serves on an advisory panel funded by DuPont to review conditions in the Delaware River. None of these activities were or are specific to benzene, and Dr. Vorhees herself was and is not involved in the MCA work.

TERA has determined that Dr Vorhees has no conflicts of interest that would disqualify her for panel membership. Her activity involving funding from Chevron in 2001, together with the past and current activities of her employer, are being disclosed to assure transparency. *TERA* does not believe these activities will impair Dr. Vorhees' scientific objectivity as a VCCEP benzene panel member.

Sponsor Presenter Biographical Sketches

Mr. Sean Hays
President
Summit Toxicology

Mr. Hays is President and co-founder of Summit Toxicology, LLP, a national toxicology and risk assessment consulting firm. Sean Hays received a B.S. in Biomedical Engineering from Texas A&M University, a M.S. in Physiology from the University of Vermont and a M.S. in Chemical Engineering from Colorado State University. Mr. Hays is a toxicologist and chemical engineer with ten years of consulting experience in pharmacokinetic modeling, exposure assessment, conducting toxicology studies, developing strategies to establish environmental and occupational exposure limits and in developing exposure and risk assessments for children exposed to chemicals. Mr. Hays has been involved in developing physiologically based pharmacokinetic (PBPK) models for a range of chemicals, and has designed animal and applied human studies to develop the data necessary to answer difficult questions concerning the regulation of chemical exposure in environmental and occupational settings. He has expertise in conducting exposure assessments for environmental, occupational, and product use scenarios and has extensive experience in interpreting biomarker data to assess exposure to compounds. His work has resulted in over 25 peer-reviewed publications and one book chapter. Mr. Hays is currently serving on one EPA Science Advisory Board panel and is serving on one of EPA's Clean Air Scientific Advisory Committee panels. He has been an invited speaker to give testimony on scientific matters before the National Academy of Science and several state legislatures. Currently, Mr. Hays is a member of the Society of Toxicology, Society of Risk Analysis, International Society of Regulatory Toxicology and Pharmacology and the American Conference of Governmental Industrial Hygienists and serves as the Vice President of the Biological Modeling Specialty Section of the Society of Toxicology. Mr. Hays has served as an *ad hoc* reviewer for scientific journals including the *Journal of Toxicology and Environmental Health, Toxicological Sciences, Chemosphere, Regulatory Toxicology and Pharmacology,* and the journal of *Integrated Environmental Assessment and Management*.

Mr. Andrew Jaques
CHEMSTAR Director
American Chemistry Council

Andrew Jaques is a Director in the CHEMSTAR group of the American Chemistry Council (ACC); he joined ACC in 1998. He manages several panels and consortia at ACC on hydrocarbon solvents, aliphatic and aromatic hydrocarbons. Prior to joining ACC, Mr. Jaques worked for the American Petroleum Institute (API) as a Regulatory Analyst in its Health and Environmental Affairs Department. He was responsible for managing health, hazard communication and industrial hygiene regulatory and research programs. Prior to this, Mr. Jaques work as a Safety and Fire Protection Associate with API, overseeing the development of safety and fire protection standards. He received a B.A. in Physics and Economics from Drew University in Madison, NJ. He also has completed all course work towards a M.P.H. in Environmental and Occupational Health from George Washington University in Washington, D.C.

Ms. Julie Panko
Managing Health Scientist
ChemRisk

Ms. Panko is a certified industrial hygienist with 18 years of professional experiencing in occupational and environmental health risk assessment. She is responsible for designing, conducting and managing projects involving complex human health risk assessment issues. Ms. Panko specializes in quantitative exposure assessment associated with occupational, residential and ambient environmental settings. Her experience includes the evaluation of potential health risks associated with chromium and other metals, benzene, perfluorooctanoic acid (PFOA), chlorinated solvents, various aromatic hydrocarbons, acetone, dioxin and polycyclic aromatic hydrocarbons. Ms. Panko also has expertise in quantitative exposure reconstruction and was responsible for an occupational historical exposure analysis of chromium workers that serves as a basis for OSHA's hexavalent chromium permissible exposure limit. Ms. Panko has completed quantitative exposure assessments and risk assessments for consumer products and environmental contaminants using a variety of mathematical modeling tools. She has also designed and implemented several simulation studies to address gaps in knowledge regarding chemical exposures. Ms. Panko received her B.S. degree in Industrial Hygiene from Ohio University.

Dr. David Pyatt
Principal
Summit Toxicology

Dr. Pyatt is a Principal and co-founder of Summit Toxicology, LLP, a national toxicology and risk assessment consulting firm. He also is an adjunct professor in the Schools of Medicine and Pharmacy at the University of Colorado Health Sciences Center in Denver, Colorado. Dr. Pyatt received a B.S. in Biological Sciences from North Carolina State University and a Ph.D. in Toxicology from the University of Colorado. He has been actively involved in toxicology research for the past 12 years, and his work has resulted in approximately 50 peer-reviewed publications and abstracts in the fields of environmental and occupational toxicology, experimental hematology, carcinogenesis and immunology. The primary focus of Dr. Pyatt's research has been to understand chemically induced blood disorders, specifically benzene and the development of secondary leukemia. Over the past 8 years, Dr. Pyatt has been an instructor and/or course director for graduate and medical courses in environmental toxicology and risk assessment, occupational and industrial health, toxicology, and immunology. He is a full member of the Society of Toxicology and the International Society of Experimental Hematology. Dr. Pyatt has served as an *ad hoc* reviewer for several scientific and technical journals, including *Blood, Experimental Hematology, Toxicology, Cell Biology and Toxicology, Toxicology and Applied Pharmacology, Toxicological Sciences* and *Occupational and Environmental Medicine*.

Dr. Ceinwen Schreiner
Toxicology Consultant
C&C Consulting

Dr. Schreiner has 35 years experience in the field of toxicology, 25 of these in the petroleum industry, with recognized expertise in genetic toxicology, reproductive and developmental toxicology, and petroleum toxicology. She is the author of more than 95 publications and presentations, many in the petroleum and petrochemical areas, and holds four patents for methods to evaluate toxicity of petroleum based materials. Dr. Schreiner worked in pharmaceutical toxicology at E.R. Squibb and Sons, Inc. and McNeil Laboratories, a division Johnson and Johnson. As vice president of the Environmental and Health Sciences research and testing laboratory for Mobil Oil Corporation, Dr. Schreiner directed activities of scientists in areas ranging from analytical chemistry to mammalian and environmental

toxicology. She is expert in designing and implementing mammalian toxicology studies in accordance with Good Laboratory Practices, assessing data, and writing and evaluating study reports. Dr. Schreiner Fellow in Academy of Toxicological Sciences and is listed in American Men & Women of Science and Who's Who in Science and Engineering. She has a broad range of experience in preparing technical papers, reviewing and interpreting research/testing results, and developing hazard assessments for products. She has served as toxicology consultant on risk assessment, regulatory and litigation/medical issues.

Appendix C

Voluntary Children's Chemical Evaluation Program (VCCEP)
Peer Consultations on Benzene
June 15-16, 2006

Public Comments

Table of Contents

Ms. Christina Cinalli
Chemist Exposure Assessment Branch
US EPA / Office of Pollution Prevention and Toxics
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cinalli.christina@epa.gov

Environmental Fate Properties

The VCCEP submission for benzene would benefit from more discussion supporting the statements about environmental fate, including persistence and partitioning. While EPA realizes that there are several detailed discussions of the environmental fate in the references listed on page 22 and in the SIAR attached as a reference, the Submitter should provide the reader with a more thorough overview, including Level III fugacity modeling results. The statement made in Section 5.3: "As demonstrated by this table, benzene is generally found in the air and its presence in water is limited by benzene's water solubility and high vapor pressure." is misleading. Whereas monitoring data may suggest benzene is most commonly found in air, Level III Fugacity modeling shows that water can be significant sink for benzene.

In the Equilibrium Criterion (EQC) Model v 1.0, benzene is provided as an example chemical. The EQC model is essentially the same as what is used in EPI Suite v3.11. The results presented in the example EQC model run is for equal releases of benzene to air water, and soil. Most of the benzene released to soil evaporates to air. So does about 1/3 of the benzene released to water. This means 2/3 of the benzene released to water stays in water where much of this is reacted (degrades) and some advected out. In table 5.3, the water solubility of benzene is characterized as "low-moderate", however, we disagree with this characterization and would characterize the solubility as "moderate". Also, the Henry's Law constant is characterized as "High" and we would characterize it as "Moderate". Here are the results of the EQC model run for benzene:

(See attached file: EQC Model Run for Benzene.doc)

Another comment on section 5.3, is as follows: "The small amount of benzene that is found in groundwater is relatively mobile, but may biodegrades if when a sufficient amount of dissolved oxygen is available. Atmospheric benzene degrades rapidly due to reaction with atmospheric hydroxyl radicals and has a residence time between a few hours and several days, depending on season and location (e.g., urban vs. rural atmosphere), depending on season."

In the High Production Volume program, the Office of Pollution Prevention and Toxics accepts the results of a Level I fugacity model, but makes it clear that results of a Level III fugacity model are preferred. The submission should include the results of Level III fugacity modeling. Level I fugacity modeling considers only equilibrium partitioning, ignoring all types of degradation. Level III fugacity modeling is more complicated than Level I fugacity modeling, and includes degradation, advection (physical movement of a substance), atmospheric deposition, etc.

Level III fugacity results can be significantly different for some chemicals and may show that the model does not predict that all of the chemicals will partition out of water at steady state. In fact, the Level III results suggest that water, soil, and sediment are the major compartments for these types of chemicals when equal, continuous emissions to air, water, and soil occur. This highlights the importance of data on emissions as well as degradation rates for all major compartments. EPI Suite v3.11 makes Level III fugacity calculations. EPI Suite v3.11 is readily available at: http://www.epa.gov/opptintr/exposure/docs/episuitedl.htm The submission states that benzene biodegrades in groundwater (although no reference is provided), but does not address the removal of benzene in sewage treatment or drinking water treatment plants. Biodegradation is a characteristic that can significantly affect environmental fate and exposure, and it is important to include both along with references.

Exposure Assessment

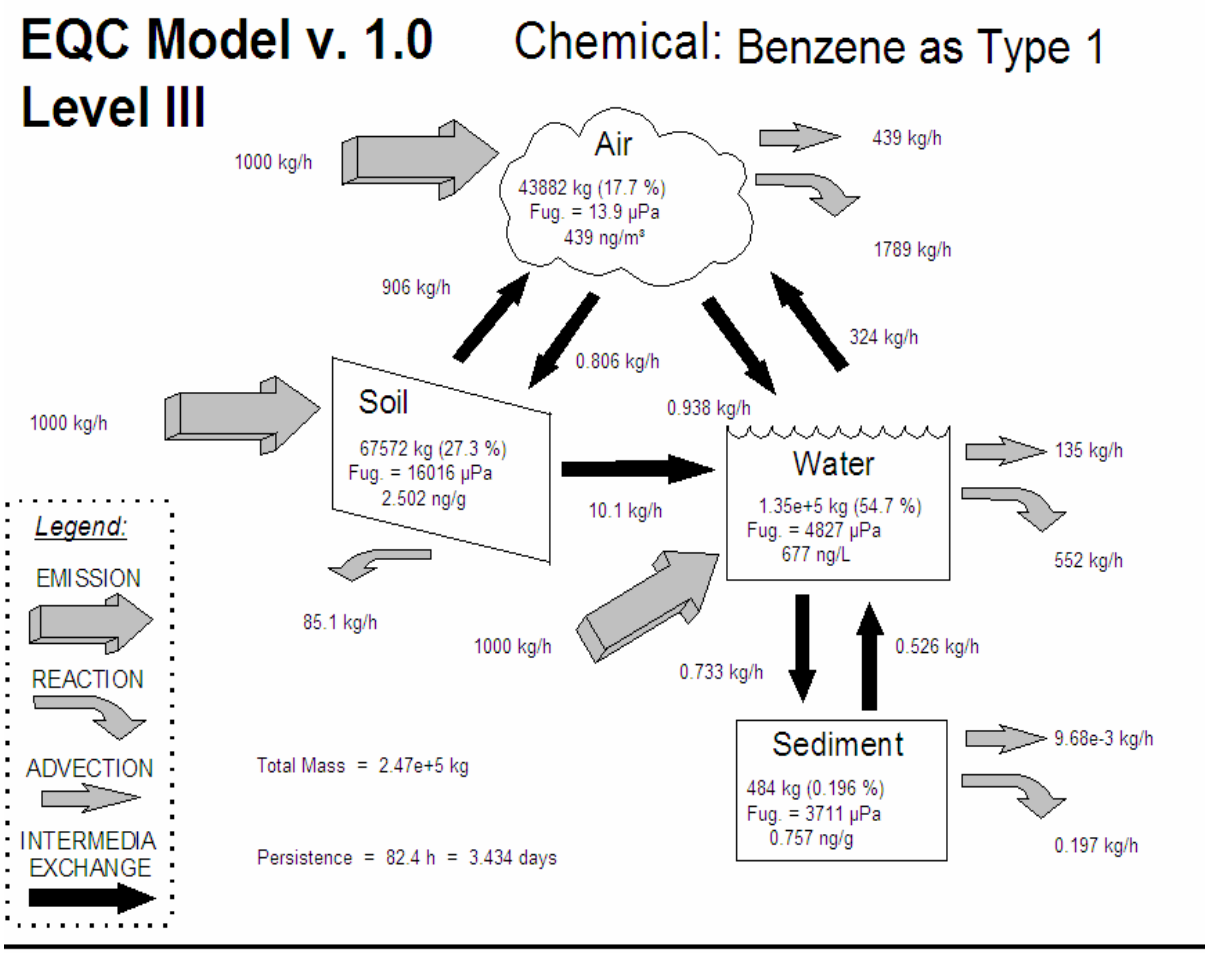
Exposure assessment in this report was based on an examination of many inhalation sources of benzene to which children might reasonably be expected to be exposed. Environmental exposures assessed in this submission include inhalation of indoor and outdoor air, consumption of food, and consumption of water. Certain "microenvironments" with potentially high exposures, such as homes where smoking occurs and the interiors of gasoline-powered motor vehicles, were also assessed.

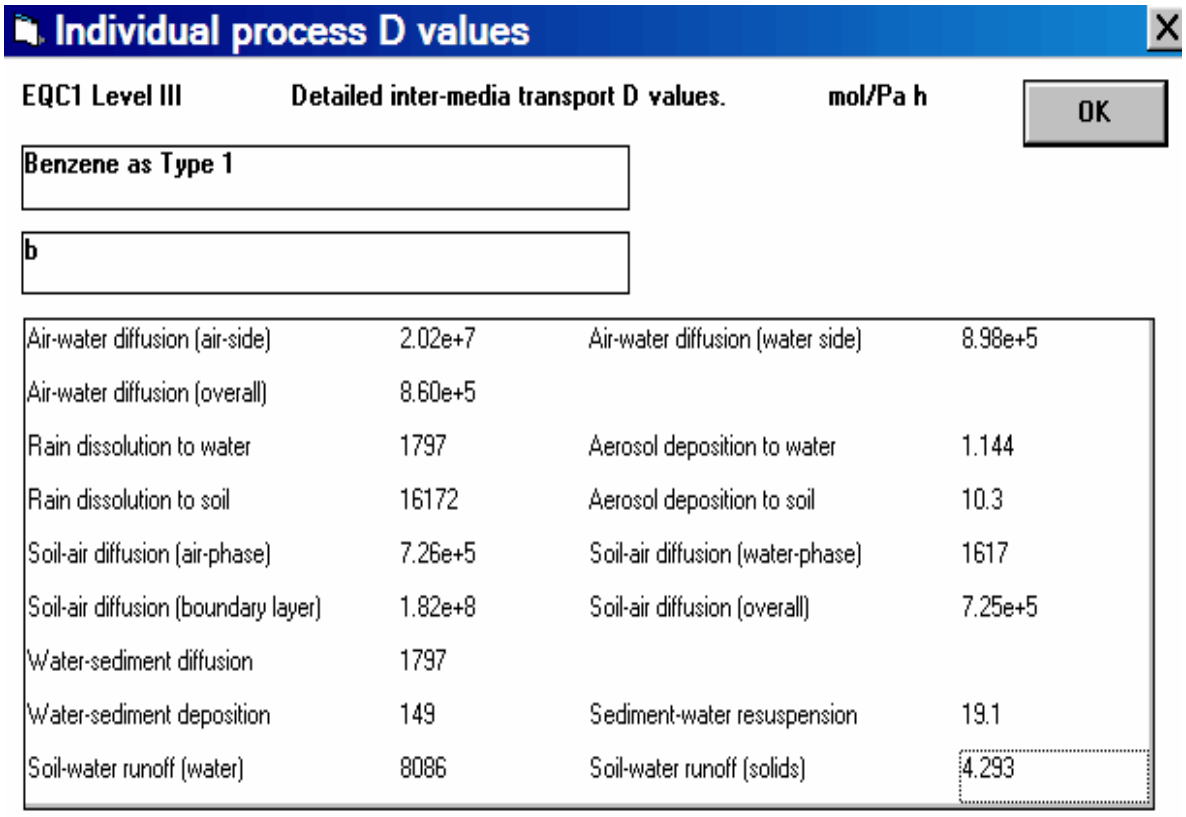
The assessment did assess exposure to the target population from tap water using monitoring data from the National Drinking Water Contaminant Occurrence Database (NCOD). Maximum, mean, median and 95th Percentile (by rank) values are presented on page A-17. However, the assessment did not address ingestion benzene in drinking water downstream from chain of commerce sources, such as manufacturing, processing and use of benzene. This exclusion should be corroborated with data, such as TRI data, which will provide information on water releases that could be linked to exposures down stream from chain of commerce sources. Additionally, the section on tap water ingestion should provide ingestion rate assumptions, specifically, did the assessors include in their assumptions the ingestion of tap water used to prepare powdered infant formula or to cook with?

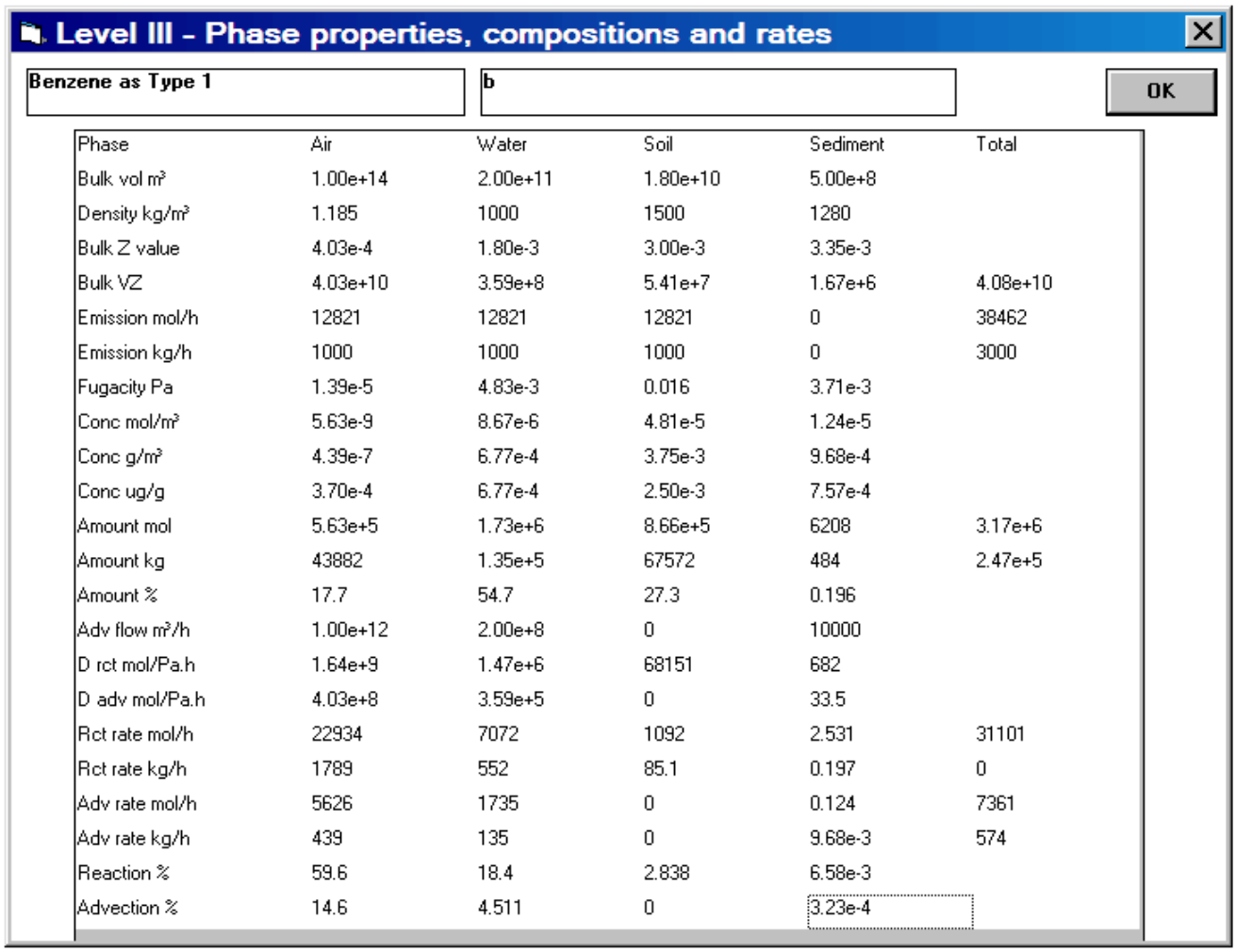
Rural and urban benzene concentrations in ambient outdoor air were derived from EPA's National Air Toxics Assessment (NATA) database and EPA's AirData database. The NATA data are from 1996 and the AirData data are from 2000. The NATA database uses air dispersion modeling to estimate ambient air concentrations from known emissions from outdoor sources. The submission does not describe the modeling process in detail, but provides a citation for the database. Page 105 of the VCCEP submission provides the typical rural and urban exposure concentrations (0.72 and 1.57 g/m3, respectively), based on the mean value of air concentrations from rural and urban counties in the NATA database. The high-end values (1.0 and 4.4 g/m3 for rural and urban, respectively) were derived from the AirData database. The rural value was obtained from the 2000 edition of the database, and the urban value was derived from the mean concentration at the monitoring station closest to the highest urban benzene emitter (Harris County, TX). The submission is a bit unclear on the use of 2000 or 2003 AirData to derive the high-end concentrations. It states that "The 2003 urban value is from 2000 AirData" and "the rural value is from 2000 AirData." It is also unclear as to why two different sources were used,

and why a rural mean value is considered a “high-end” exposure in one database (AirData) and a typical exposure in another database (NATA). Clarification of these issues would be useful.

EQC Model Run for Benzene.doc




Individual process D values
EQC1 Level III
Detailed inter-media transport D values.
mol/Pa h
OK
Benzene as Type 1
b
Air-water diffusion (air-side) 2.02e+7
Air-water diffusion (water side) 8.98e+5
Air-water diffusion (overall) 8.60e+5
Rain dissolution to water 1797
Aerosol deposition to water 1.144
Rain dissolution to soil 16172
Aerosol deposition to soil 10.3
Soil-air diffusion (air-phase) 7.26e+5
Soil-air diffusion (water-phase) 1617
Soil-air diffusion (boundary layer) 1.82e+8
Soil-air diffusion (overall) 7.25e+5
Water-sediment diffusion 1797
Water-sediment deposition 149
Sediment-water resuspension 19.1
Soil-water runoff (water) 8086
Soil-water runoff (solids) 4.293



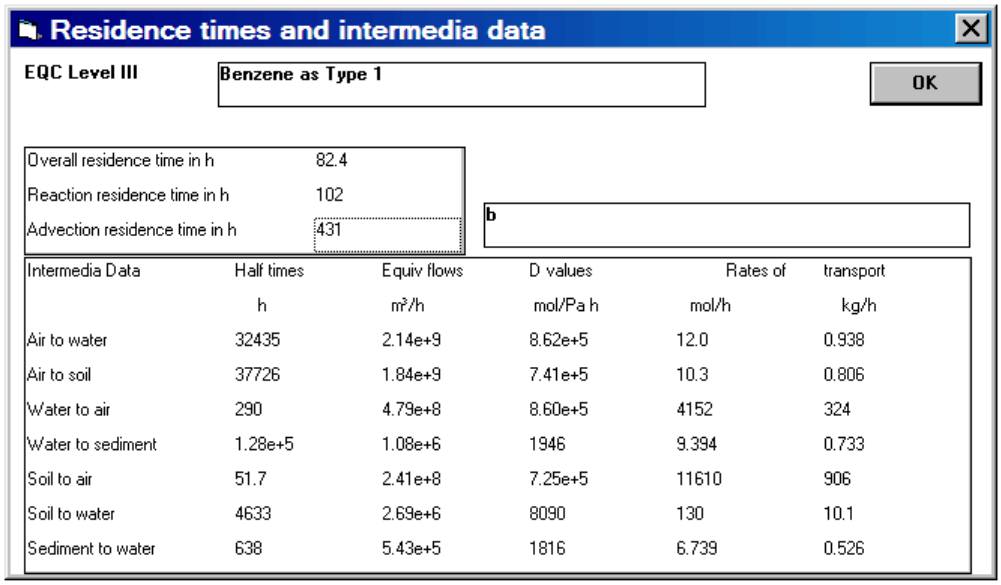
Level III - Phase properties, compositions and rates

Benzene as Type 1

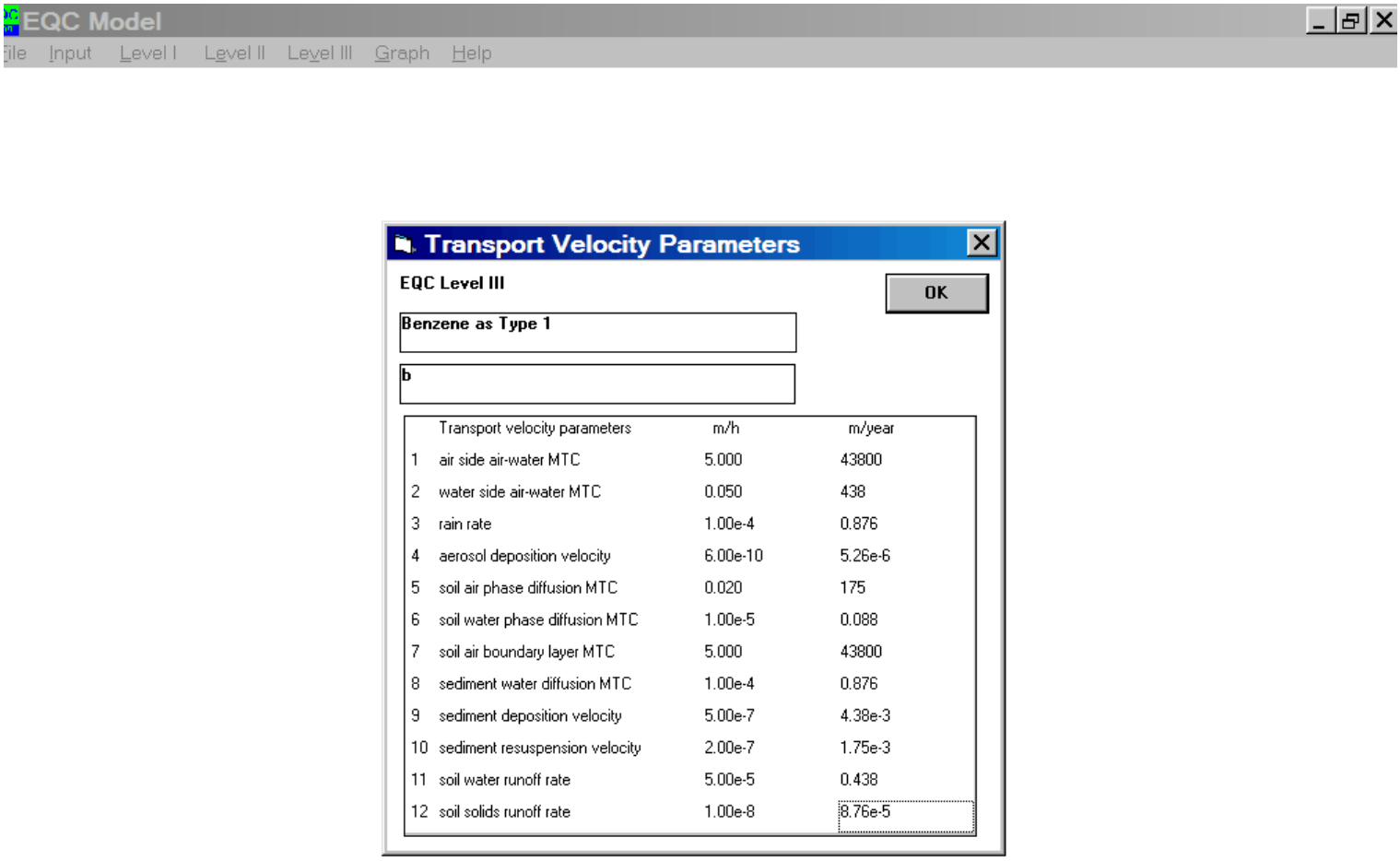
b

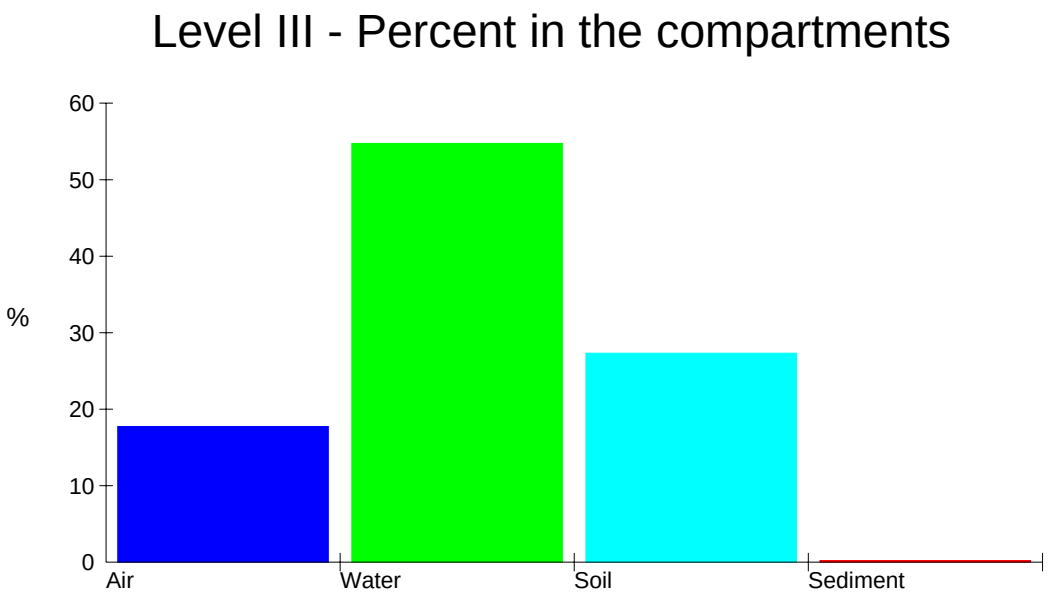
OK

Phase	Air	Water	Soil	Sediment	Total
Bulk vol m³	1.00e+14	2.00e+11	1.80e+10	5.00e+8	
Density kg/m³	1.185	1000	1500	1280	
Bulk Z value	4.03e-4	1.80e-3	3.00e-3	3.35e-3	
Bulk VZ	4.03e+10	3.59e+8	5.41e+7	1.67e+6	4.08e+10
Emission mol/h	12821	12821	12821	0	38462
Emission kg/h	1000	1000	1000	0	3000
Fugacity Pa	1.39e-5	4.83e-3	0.016	3.71e-3	
Conc mol/m³	5.63e-9	8.67e-6	4.81e-5	1.24e-5	
Conc g/m³	4.39e-7	6.77e-4	3.75e-3	9.68e-4	
Conc ug/g	3.70e-4	6.77e-4	2.50e-3	7.57e-4	
Amount mol	5.63e+5	1.73e+6	8.66e+5	6208	3.17e+6
Amount kg	43882	1.35e+5	67572	484	2.47e+5
Amount %	17.7	54.7	27.3	0.196	
Adv flow m³/h	1.00e+12	2.00e+8	0	10000	
D rct mol/Pa.h	1.64e+9	1.47e+6	68151	682	
D adv mol/Pa.h	4.03e+8	3.59e+5	0	33.5	
Rct rate mol/h	22934	7072	1092	2.531	31101
Rct rate kg/h	1789	552	85.1	0.197	0
Adv rate mol/h	5626	1735	0	0.124	7361
Adv rate kg/h	439	135	0	9.68e-3	574
Reaction %	59.6	18.4	2.838	6.58e-3	
Advection %	14.6	4.511	0	3.23e-4	



Intermedia Data	Half times h	Equiv flows m³/h	D values mol/Pa h	Rates of mol/h	transport kg/h
Air to water	32435	2.14e+9	8.62e+5	12.0	0.938
Air to soil	37726	1.84e+9	7.41e+5	10.3	0.806
Water to air	290	4.79e+8	8.60e+5	4152	324
Water to sediment	1.28e+5	1.08e+6	1946	9.394	0.733
Soil to air	51.7	2.41e+8	7.25e+5	11610	906
Soil to water	4633	2.69e+6	8090	130	10.1
Sediment to water	638	5.43e+5	1816	6.739	0.526


EQC Model
File Input Level I Level II Level III Graph Help
Transport Velocity Parameters
EQC Level III
OK
Benzene as Type 1
b
Transport velocity parameters m/h m/year
1 air side air-water MTC 5.000 43800
2 water side air-water MTC 0.050 438
3 rain rate 1.00e-4 0.876
4 aerosol deposition velocity 6.00e-10 5.26e-6
5 soil air phase diffusion MTC 0.020 175
6 soil water phase diffusion MTC 1.00e-5 0.088
7 soil air boundary layer MTC 5.000 43800
8 sediment water diffusion MTC 1.00e-4 0.876
9 sediment deposition velocity 5.00e-7 4.38e-3
10 sediment resuspension velocity 2.00e-7 1.75e-3
11 soil water runoff rate 5.00e-5 0.438
12 soil solids runoff rate 1.00e-8 8.76e-5


Level III - Percent in the compartments
%
60
50
40
30
20
10
0
Air
Water
Soil
Sediment

Appendix D

Voluntary Children's Chemical Evaluation Program (VCCEP)
Peer Consultations on Benzene
June 15-16, 2006

Sponsors' Presentation Slides

Benzene Tier 1
VCCEP Assessment

American Chemistry Council
BTX VCCEP Consortium

Outline for Presentations

Introductions/Background:
Andrew Jaques, ACC Consortium Manager

Hazard Assessment:
Animal Data - Dr. Ceinwen Schreiner, C&C Consulting
Human Data – Dr. David Pyatt, Summit Toxicology

Exposure Assessment:
Julie Panko, ChemRisk

Risk Assessment:
Sean Hays, Summit Toxicology

VCCEP Tier 2 Data Needs Assessment:
Andrew Jaques, ACC Consortium Manager

Benzene Tier 1 VCCEP Sponsors

BP
Chevron Phillips Chemical Company LP
The Dow Chemical Company
E.I. du Pont de Nemours & Company
Equistar Chemicals, LP
ExxonMobil Chemical Company
Flint Hills Resources, LP
Marathon Petroleum LLC
Shell Chemical LP
Sterling Chemical Company
Sunoco, Inc.
TOTAL Petrochemicals, U.S.A.

VCCEP Selection Basis

- Benzene was selected for the VCCEP pilot program because of:
  - Human biomonitoring databases (NHANES, NHEXAS)
  - Exposure studies/databases (TEAM, indoor air studies, drinking water (NCOD))
  - OECD SIDS Program Evaluation

Chemical Background

- High volatility/partitions mostly to air (99.9%).
- Low/moderate water solubility (1.8 g/L @ 25^{o}C).
- Biodegradable.
- Low bioaccumulation/bioconcentration.
- TRI emissions mostly to air (93%); emissions have been reduced 75% from 1990 to 2003.

Chemical Background (2)

- Pure benzene is used as chemical intermediate in the production of cumene, cyclohexane, ethylbenzene, nitrobenzenes and other chemical intermediates.
- Benzene is present in unleaded automobile gasoline at about 1%. Heavier fuels such as jet fuel, kerosene, and diesel fuel have much less benzene content, generally less than 0.02%.
- By-product of combustion (mobile sources, biomass burning, cigarette smoke).
- Benzene has not been used as a solvent in the U.S. for decades.
- There have been numerous previous regulatory and scientific reviews of benzene.

Regulatory Overview

- Benzene is regulated under a number of environmental, health, and safety regulations, including:
  - Federal, state, and local air pollution regulations;
  - Volatile Organic Compound (VOC) regulations;
  - Toxic Release Inventory (TRI) emission reporting;
  - Clean Water and Safe Drinking Water regulations;
  - Occupational safety and health regulations;
  - Gasoline regulations limiting benzene content.
- Additional benzene regulation proposed for mobile sources.

Benzene Human Hazard Assessment

American Chemistry Council Good Chemistry Makes It Possible

June 15, 2006
TERA, Cincinnati, Ohio

Presenter: David Pyatt, Ph.D.
Summit Toxicology, L.L.P.
University of Colorado SOP, SOM

Benzene Human Hazard Data

Acute

- Narcosis, non-specific CNS toxicity

Chronic

Dose related effects on the blood and bone marrow

- Various cytopenias
- Aplastic anemia and pancytopenia
- Myelodysplasia (MDS)
- Acute myeloid leukemia

Leukemia Classification

Disease Progression

Acute vs. Chronic

Cell of Origin

Myeloid vs. Lymphoid

4 Major Types:

- **AML (ANLL) - Acute myeloid (non-lymphocytic) leukemia**
- **CML - Chronic myeloid leukemia**
- **ALL - Acute lymphocytic leukemia**
- **CLL - Chronic lymphocytic leukemia**

Risk Factors Associated with the Development of AML

-AML can arise secondary or *de novo* (idiopathic)
-80-90% of all AML have no readily identifiable cause

Chemotherapy (therapy related, t-AML, t-ANLL)

- **Alkylating Agents**
  Melphalan, busulfan, nitrogen mustard
- **Topoisomerase Inhibitors**
  Etoposide, doxorubicin, bimolane, others

Ionizing Radiation (also associated with ALL, CML, solid tumors)
Chronic, high dose exposure to benzene
Smoking
Increased age
Myelodysplasia

Animal Models for Benzene Toxicity

Non-cancer

There is fairly good concordance between experimental animals and humans regarding non-cancer hematopoietic toxicity.

Cancer

Less reliable, as rodents do not typically develop AML. However, the Tg.AC mouse has potential (route of administration is important and it contains the *v-ras* oncogene).

Benzene Metabolism

It is well established that benzene metabolism is required for toxicity.

Phase 1

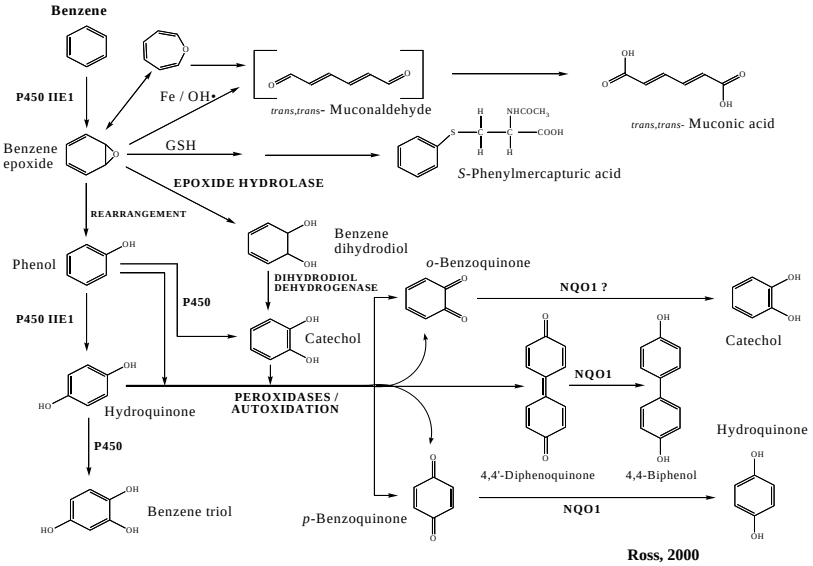
- **Primary hepatic oxidation (CYP2E1) and 'bioactivation' forms benzene epoxide, a reactive intermediate**
- **Subsequent oxidation likely occurs in the bone marrow (myeloperoxidase)**

Phase 2

Includes a variety of enzymatic reductions and detoxification steps (also occurring in the liver and bone marrow)

Polymorphisms associated with altered response to benzene have been reported in both Phase 1 and 2 enzymes (e.g. CYP2E1, NQO1, GST)

Benzene Metabolism



US EPA IRIS Values Established for Benzene

Non-cancer (updated 2003)

- **Reference Concentration (RfC = 3.0 X 10^{-2} mg/m^3)**
- **Absolute Lymphocyte Count (ALC)**
- **Rothman *et al.* (1996)**

Cancer (established in 1998)

- **Cancer Potency Factor**
- **Leukemia**
- **'Pliofilm' cohort**
- **Infante, 1977; Rinsky, 1981; Rinsky, 1987**

US EPA IRIS Key Study: Non-Cancer Risk

Rothman *et al.* (1996)

- **44 workers and age match controls**
- **Median exposure duration = 6.3 yrs**
- **Median TWA = 31 ppm**
- **Exposed Cohort was divided into 2 groups (<31 ppm, >31 ppm)**
- **Median TWA was 13.6 and 91.9 ppm, respectively**
- **From the <31 ppm group, workers were selected with no exposures over 31 ppm. Median TWA of this sub-group = 7.6 ppm (range 1-20 ppm)**
- **Only ALC was statistically significantly depressed in this 'low' dose group (1.6 X 10^3/uL)**
- **Effects on ALC were not dependent upon exposure duration (per investigators)**

Rothman et al., (1996) Cont.

- **ALC values for workers within the selected exposure group were within the normal hematology range (2.5 X 10^3/uL, range = 1-4.8)**
- **There was no evidence of functional impairment associated with this decrease**
- **Not all studies have reported that lymphocytes are the most sensitive cell type**
- **Peripheral cytopenias reported in workers occupationally exposed to benzene typically have a rapid onset and are frequently reversible**

Post-IRIS Studies of Hematological Changes in Benzene Exposed Workers

Qu, et al., (2002) Hematological Changes Among Chinese Workers With a Broad Range of Benzene Exposures. Am. J of Ind. Med 42:275-285.

Lan et al., (2004) Hematotoxicity in Workers Exposed to Low Levels of Benzene. Science 306:1774-1776.

Tsai, et al., (2004) A Hematology Surveillance Study of Petrochemical Workers Exposed to Benzene. Regulatory Toxicology and Pharmacology 40:67-73.

Quitt, et al., (2004) Autonomous Growth of Committed Hematopoietic Progenitors From Peripheral Blood of Workers Exposed to Low Levels of Benzene. JOEM 46:27-29.

Sul, et al., (2005) DNA Damage in Lymphocytes of Benzene Exposed Workers Correlates with *trans, trans*-Muconic Acids and Breath Benzene Levels. Mutation Research 582: 61-70.

Brandao, et al., (2005) Phenotype Analysis of Lymphocytes of Workers with Chronic Benzene Poisoning Immunology Letters 101(1): 65-70.

US EPA IRIS Cancer Assessment: 'Pliofilm' Cohort

- **NIOSH sponsored "Pliofilm" study in 3 facilities in Ohio**
- **Retrospective cohort mortality study**
- **Original cohort: 748 workers, exposed at least one day from 1940-1949**
  - **Infante, 1977; Rinsky et al, 1981**
- **Rinsky 1987; update to include workers followed through 1981**
  - **9 'leukemia' cases vs. 2.7 expected (SMR = 337, 95%CI = 154-641)**
  - **Statistically significant at 200 ppm-yrs (SMR = 1186, 133-4285)**
- **Paxton, 1994; update to include workers followed through 1987**
  - **14 'leukemia' cases vs. 3.89 (SMR = 360, 95% CI = 197-604)**
  - **Significance level varied depending on exposure estimated used**
- **Wong, 1995; analysis specific to AML through 1987**
  - **6 AML cases vs. 1.19 (SMR = 5.03, 95% CI = 1.81-10.97)**
  - **Statistically significant at 200 ppm-yrs (SMR = 27.21, 95% CI = 3.29-98.24)**
- **Rinsky, 2002; update to include workers followed through 1996**
  - **15 'leukemia' cases vs. 5.87 (SMR = 2.56, 95% CI = 1.43-4.22)**
  - **Statistically significant at 400 ppm-yrs (SMR = 23.96, 95% = 4.82-78.51)**

Pliofilm Cohort Studies

- **All workers with 'leukemia' worked prior to 1950 and most were employed prior to 1945.**
- **Monitoring data for these periods was poor, especially prior to 1946.**
- **Many efforts to refine quantitative exposures have been undertaken, with relatively consistent results.**
  - **Crump, 1984**
  - **Rinsky, 1987**
  - **Paustenbach, 1992**
  - **Schnatter, 1996**
  - **Williams, 2004**

Study Selected by US EPA IRIS for Benzene Cancer Risk

- **Rinsky, 1987**
  - **•Reasonable estimates of exposure**
  - **•Reasonable understanding of job activities**
  - **•Wide range of exposures**
  - **•Relative lack of confounding chemicals**
- **Carcinogenic risk of inhaled benzene per US EPA IRIS (updated 2003)**

  7.1×10^{-3} to 2.5×10^{-2} per ppm
- **This was based on the linearized multi-stage model**
- **Range of unit risks is based on exposure estimates from Crump and Allen, 1984 (lowest exposure estimate) and Paustenbach, 1992 (highest exposure estimate)**

Post-IRIS Studies of Leukemia Risk in Benzene Exposed Workers

•Adegoke, et al., (2003) Occupational History and Exposures and the Risk of Adult Leukemia in Shanghai. Ann Epidemiology 13:485-494.

•Glass, et al., (2003) Leukemia Risk Associated With Low-Level Benzene Exposure. Epidemiology 14(5):569-577.

•Sorahan, et al., (2005) Cancer Risks in a Historical UK Cohort of Benzene Exposed Workers. Occup Environ Med 62: 231-236

Human Genotoxicity Data

- **Results from standard genotoxic assays are equivocal and can vary considerably with metabolite**
  - **DNA adduct formation**
  - **Micronuclei formation**
  - **SCE**
  - **DNA breaks (single or double)**
- **More consistent evidence for clastogenicity or chromosome damage**
  - **Structural and numerical**
  - **Reported in *in vitro* assays**
  - **Reported in benzene-exposed worker populations**
  - **Potential involvement of chromosomes 5,7 and/or 8**
- **The role that genotoxicity plays in benzene induced hematopoietic effects has not been established.**

Reproductive and Developmental Toxicity

Reproductive

- **Menstrual abnormalities have been reported.**
- **The literature is extremely inconsistent and existing studies are weakened by significant confounders and poor or non-existent exposure data.**

Developmental

- **Birth defects and spontaneous abortions have been inconsistently reported.**
- **Significant confounding factors exist.**

Collectively, there is insufficient data to establish a reproductive or developmental effect associated with benzene exposure

Parental Exposures and Childhood Leukemia

- **There have been many studies on potential risk factors for childhood leukemia. These include infectious agents, diet, smoking, alcohol consumption, drug use during pregnancy, environmental exposures and others. There is no consistent evidence to support a link with any of these factors and childhood leukemia.**
- **There have also been scattered reports of maternal or paternal exposures to benzene and potential associations with childhood leukemia (typically ALL and AML combined). Most are negative, particularly for childhood ALL.**
- **One study suggested a potential relationship between maternal exposure to benzene and childhood AML (Shu, et al. 1988). No exposure information was provided and this finding has not been confirmed by independent investigation.**
- **It is not clear what role maternal or paternal exposures to benzene (even high occupational exposures) contribute to the development of childhood leukemia, including childhood AML.**

Conclusions

- **Mechanism of action (for cancer or non-cancer toxicity) is still unknown.**
- **There is no generally accepted animal model for benzene induced AML.**
- **There is a wealth of human data for both cancer and non-cancer endpoints.**
- **Lymphocytopenia has been reported to be the most sensitive non-cancer endpoint.**
- **High dose, chronic exposure to benzene has been positively associated with the development of AML.**
- **There is no positive association between benzene exposure and reproductive and/or developmental toxicity.**
- **Studies of the potential association between parental exposures to benzene the development of childhood leukemia are equivocal.**

Benzene VCCEP Hazard Assessment: Animal Toxicology

June 15, 2006

Dr. Ceinwen Schreiner

Hazard Assessment: Introduction

Extensive toxicology data are available on benzene to address VCCEP Hazard Endpoints.

Toxicity Tests Tiers

- **Tier 1**
  - Acute Oral or Inhalation
  - *In vitro* Gene Mutation: Bacterial Reverse Mutation Assay
  - Combined repeated dose toxicity study with reproductive/developmental toxicity screen OR Repeat dose oral study and Reproductive toxicity [1-generation]
  - *In vitro* Chromosome aberration assay OR *In vivo* chromosome aberration assay OR *In vivo* Mammalian erythrocyte micronucleus assay

Toxicity Tests Tiers (cont.)

- **Tier 2**
  - 90 day Subchronic toxicity study
  - Reproductive and fertility effects
  - Prenatal developmental toxicity
  - *In vivo* chromosome aberration assay OR *In vivo* Mammalian erythrocyte micronucleus assay
  - Immunotoxicity
  - Metabolism and Pharmacokinetics
- **Tier 3**
  - Carcinogenicity or Chronic toxicity/carcinogenicity
  - Neurotoxicity screening battery
  - Developmental neurotoxicity

All Tier 1 Endpoints are met

Hazard Classification

- Acute oral [rat]:
  - LD50 > 2g/kg — minimally toxic
- Acute dermal [rabbit, guinea pig]:
  - LC50 > 8.3g/kg — non-toxic
- Acute inhalation [rat]: 4 hr exposure
  - LC50 > 44.5mg/L [13,700ppm] — non-toxic
- Skin irritant
- Moderate eye irritant

All Tier 1 Endpoints are met (cont.)

- **Genetic Toxicity *In Vitro***
  - Bacterial assays: Standard - Negative ±S9
  - Bacterial assays: vapor or microsuspension - Positive +S9
  - Mammalian Cells : Positive - chromosomes, UDS, SCE
- Repeat Dose Screening studies are superceded by Tier 2 studies.

Tier 2 Endpoints

- **Genetic Toxicity *In Vivo***
  - Micronucleus assay: Positive
    Inhalation [single 6hr exposure] (Erexson et al, 1986)
    LOAEL rats = 1ppm; LOAEL mice = 10ppm
    Oral, mice [4 months] (MacGregor et al., 1990)
    LOAEL females = 50mg/kg/day; LOAEL males = 25mg/kg/day
  - Chromosome aberrations: Positive
    Inhalation: rats, 6hr exposure LOAEL = 100ppm (Styles/Richardson, 1984)
    Oral: rats, single dose LOAEL = 132mg/kg (Fujie et al., 1992)
  - Dominant Lethal assay, Rats: Negative
    Inhalation: rats, 6hr/d, 10 weeks NOAEL = 300ppm (API, 1980)
    no increase in pre- or post-implantation losses

Transplacental Toxicity

- **Genetic toxicity *In Vivo***
  - Cytogenetic effects in fetal organs correlate with stages of hematopoietic development in rodents.
  - Sensitivity greatest at Gestation Days (GD) 13-15.
  - Oral, rats: 0, 80mg/kg on GD 13 [Ciranni et al., 1991]
    Increased incidence of micronucleated polychromatic erythrocytes (PCE) similar in bone marrow of dams and fetal livers.
  - Oral, mice: 0, 50 -75mg/kg/d on GD 17-19 [Harper et al., 1989]
    No increase in micronucleated-PCE of pregnant dams or fetuses.
  - Intraperitoneal, mice: 0, 109-874mg/kg on GD14 [Ning et al.,1991]
    LOAEL fetus = 219mg/kg, increased micronucleated-PCE in fetal livers.
    LOAEL dam = 437mg/kg, increased micronucleated-PCE in bone marrow.

Tier 2 Endpoints (cont.)

- **Repeat Dose Studies**
  - **Inhalation**

90 days: 0, 1.0, 10, 30, 300ppm [Ward et al., 1995]

Rats: LOAEL = 300ppm, decreased WBC count and femoral cellularity
Mice: LOAEL = 300ppm, extensive hematologic changes
Rats/Mice: NOAEL = 30ppm

1-8 weeks: 0, 1, 5, 10, 100, 200ppm [Farris et al., 1997]

Mice: LOAEL = 100ppm, reduced femoral bone marrow cellularity, persistent reduction in splenic and femoral lymphocytes.
Cellularity levels returned to control values after 25 days recovery for mice exposed to 100ppm for 4 weeks.
NOAEL = 10ppm

Tier 2 Endpoints (cont.)

- **Repeat Dose Studies: (cont.)**
  - **Oral: 17 week study** [NTP, 1986; Huff et al., 1989]

Doses: actual 0, 18 - 429mg/kg/d (nominal 25 - 600mg/kg/d) for 17 wks or 0, 143, 429mg/kg/d (0, 200, 600mg/kg/d) for 60 days

Rat: LOAEL female = 18 (25)mg/kg/d, hematologic effects
LOAEL male = 143 (200)mg/kg/d, hematologic effects
Body weight depression =/> 143mg/kg/d

Mice: LOAEL male = 36 (50)mg/kg/d, hematologic effects
LOAEL female = 286 (400)mg/kg/d, hematologic effects
Body weight depression =/> 71(100)mg/kg/d

Transplacental Toxicity

- **Hematopoietic toxicity**
  - **Inhalation, mice**: 0, 5-20ppm [Keller and Snyder, 1986]

    Exposure: GD 6-15, terminated on GD 16, postnatal day 2, 6wk
    LOAEL = 5ppm, changes in erythropoietic (CFU-E)and blast precursor cells (BFU-E) at GD 16. Effects varied at different exposures and ages.
    Alteration of hematopoietic progenitor cells persisted for at least 10wks after birth.
  - **Inhalation, mice**: 0,10ppm [Corti and Snyder, 1996]

    Exposure: GD 6-15; benzene, or benzene+ 10% ethanol in drinking water or 10% ethanol alone.
    Depression of CFU-E in livers of male fetuses at GD16 in benzene and benzene + ethanol groups.

Tier 2 Endpoints (cont.)

- **Developmental Toxicity:**
  - **Inhalation, Rats** [Kuna and Kapp, 1981]

    0, 10, 50, 500ppm, 7hr/d from GD 6-15

    LOAEL dam & fetus = 50ppm, decreased body wt, skeletal variations

    NOAEL dam & fetus = 10ppm

    Similar effects reported in mice and rabbits
  - **Oral, Rats** [Exxon Chemical Co., 1986]

    0, 50, 250, 500, 1000mg/kg/d from GD 6-15

    LOAEL dam & fetus = 500mg/kg/d, decreased body wt & wt gain

    NOAEL dam & fetus = 250mg/kg/d, no external malformations

    Effects primarily seen at maternally toxic or stressful levels.

Tier 2 Endpoints (cont.)

- **Reproductive Toxicity**:
  - **Female Rat Fertility** [Kuna et al., 1992]

    Doses 0, 1, 30, 300ppm, 8 wks premating, 2 wks mating, 6hr/d, 5d/wk,
    Gest. day 0-20, Lact. Day 5-20, 6hr/d, 7d/wk

    Results: Parental systemic & Reproductive NOAEL = 300ppm
    - F1 offspring; reduced body and organ wt trends
    - LOAEL female pups= 300ppm, decreased liver weight.
    - NOAEL female pups = 30ppm; NOAEL male pups = 300ppm
    - No malformations
  - **Repeat dose studies:** Male rats appear resistant to effects on reproductive organs (Ward et al, 1985; NTP, 1986)

    Male mice show testicular effects at high doses (Ward et al, 1985; Spano et al., 1989)

Tier 2 Endpoints (cont.)

- **Immunotoxicity**
  - **Drinking water, mice** [Hsieh et al, 1988]

    Doses: 0, 31, 166 or 790mg/L (0, 8, 40, 180mg/kg/d), 28 days
    LOAEL = 8mg/kg/d, antibody responses, dec. spleen, thymus wt
  - **Inhalation, mice** [Rosenthal & Snyder, 1985]

    Doses: 0 - 300ppm, 5 days then pathogen infection
    LOAEL = 30ppm, delayed cell mediated immune response
    NOAEL = 10ppm
  - Effects in immune system occur at doses that produce hematotoxicity.

Tier 2 Endpoints (cont.)

- **Toxicokinetics and Metabolism**
  - Absorption rapid by inhalation and ingestion; readily absorbed dermally but significant amount evaporates.
  - Distribution rapid throughout body, partitions into fatty tissue.
  - Toxicity of benzene mediated by metabolites, not parent compound.
  - Primary metabolism occurs in liver; extrahepatic metabolism in lung and bone marrow.
  - Major metabolites in animals and humans are phenol, hydroquinone and catechol.
  - Elimination of unmetabolized benzene by exhalation. Urinary excretion of metabolized benzene as conjugated derivatives [sulfate and glucuronide].

Tier 3 Endpoints

- **Chronic Toxicity/Carcinogenesis: Rats**
  - **Oral, 104 weeks**: [NTP, 1986, Huff et al., 1989]

    Females 0, 18 -71mg/kg/d actual, (25 -100mg/kg/d nominal)

    Males 0, 36 -143mg/kg/d actual (50 - 200mg/kg/d nominal)

    Systemic toxicity: leukopenia/lymphocytopenia

    Carcinogenicity: Zymbal gland, oral cavity tumors (both sexes),
    skin tumors (males only)

    LOAEL female = 18 (25)mg/kg/d;

    LOAEL male = 36 (50)mg/kg/d

Tier 3 Endpoints (cont.)

- **Chronic Toxicity/Carcinogenesis: Mice**
  - **Oral, 104 weeks**: [NTP, 1986, Huff et al., 1989]

    Both sexes 0, 18 -71mg/kg/d actual (25 -100mg/kg/d nominal)

    Systemic toxicity: leukopenia/lymphocytopenia

    LOAEL both sexes = 18 (25)mg/kg/d

    Carcinogenicity:

    LOAEL females = 36 (50)mg/kg/d, lymphoma, Zymbal gland, ovary, mammary tumors and alveolar/bronchial adenomas.

    NOAEL females = 18 (25)mg/kg/d

    LOAEL males = 18 (25)mg/kg/d, lymphoma, Zymbal gland, Hardarian gland prepuptial gland tumors, alveolar/bronchial adenomas.

Tier 3 Endpoints (cont.)

- **Adult Neurotoxicity**
  - **Inhalation, Mice** [Dempster et al, 1984]

    Doses: 0, 100 - 3000ppm 6h/d for # days x conc. = 3000ppm

    Results: Effects on lymphocytes and circulating RBC at exposures of 100ppm x 5 -10 days and above.

    Neurobehavioral effects: Maximum milk licking at 300ppm x 7-8 days. Hindlimb grip strength decreased at 1000ppm x 1 day.
  - **Inhalation, Mice**, male [Evans et al., 1981]

    Doses: 0, 300, 900ppm, 6h/d for 5 days, 2 week recovery

    300ppm - increased activity; 900ppm - narcosis
  - Effects occur at doses that also produce hematotoxicity

Hazard Conclusions

- Acutely non-toxic by dermal or inhalation routes and minimally toxic by oral route of exposure according to hazard classification
- Irritating to eye and skin
- Clastogenic in animals
- Induces leukopenia and lymphocytopenia in animals
- Induces solid tumors in animals
- Immunotoxic and neurotoxic effects occur at doses similar to or higher than those causing hematotoxicity

Hazard Conclusions (cont.)

- Developmental toxicity occurs primarily at doses inducing maternal toxicity or stress
- Reproductive performance and fertility unaffected by exposure to benzene
- Transplacental effects demonstrated for hematopoietic and genetic endpoints
- Extensive toxicity data are available to address VCCEP hazard endpoints

Benzene VCCEP
Exposure Assessment

June 15, 2006

Julie Panko,
ChemRisk

Overview

- Focused on pathways and routes of exposure relevant to children and prospective parents.
- Grouped exposures by
  - Background sources of exposure
  - Source-specific exposures
- Assessed inhalation, ingestion and dermal exposure routes
  - Typical (average or mean exposure concentrations or exposure parameters)
  - High-end (90^{th} or 95^{th} percentile exposure concentration or exposure parameters)

Age Groups Included in Exposure Assessment

- Children's age groupings were based primarily on activity patterns, and EPA cancer guidance
- Prospective parents were included for evaluation of human milk pathway relevant for infants and potential male reproductive effects.

Category	Age Group
Children	< 1 yr
	1 to < 2 yr
	2 to < 6 yr
	6 to < 16 yr
	16 to < 19 yr
Prospective Parents	19 to < 36 yr

Background Exposure Sources

- Ambient Air
  - Outdoor air
  - Indoor air
- Dietary
  - Food
  - Water
  - Human Milk

Evaluation of Source-Specific Exposures

- Tobacco smoke
- Gasoline
- Consumer Products
- Occupational

Background: Ambient Air – Outdoor

- Reviewed published literature and government databases as sources of exposure data.
- For typical concentrations, used EPA's NATA database
- For high-end concentrations, urban and rural measured data from counties where the highest TRI reporting facilities are located.

Outdoor Air Benzene Concentrations in µg/m3 (and ppb)		
Setting	**Typical**	**High-End**
Rural	0.72 (0.23)	1.0 (0.31)
Urban	1.57 (0.49)	4.4 (1.4)

*Since the time of this analysis, the EPA released an updated NATA using the 1999 emissions inventory. The updated NATA for benzene indicated that the predicted 1999 ambient air concentrations of benzene nationwide and for the 'all urban' and 'all rural' counties were similar to the 1996 modeled estimates.

Background: Ambient Air – Indoor Typical

- Reviewed the published literature
  - Outdoor influences and indoor sources contribute to overall indoor concentrations
  - Indoor > outdoor
  - Primary sources are gasoline and combustion sources (primarily tobacco smoke)
  - Used average of medians from studies from the mid 1990s to the present
- Typical indoor benzene = 2.5 µg/m3(0.78 ppb)

Background: Ambient Air – Indoor High-End

- Reviewed the published literature
  - Homes with attached garages have higher range of indoor benzene concentrations than homes without
  - Garage sources include evaporative emissions from autos, small engine equipment and gasoline storage containers
  - Adgate et al. (2004) was best available study for determining high-end indoor benzene concentration
- High-end indoor benzene = 11.5 µg/m3 (3.6 ppb)

Background: Ambient Air - Alaska

- Reviewed the published literature
  - Indoor concentrations in Alaska are higher than those measured in attached garage studies
  - Benzene content in Alaskan gasoline is higher than in lower 48 states and has been declining
  - Homes and garages are better insulated and have lower air exchange rates
  - Used mean from Morris et al. (2004)
- Alaska indoor benzene = 24.2 µg/m3 (7.6 ppb)

Background: Dietary – Food

- Exposure concentrations for food were derived from FDA's Total Diet Survey (2003).
- Used Lifeline™ Version 2.0 to model aggregate exposures to benzene from food intake.

Ingestion of Benzene from Foods (mg/kg-d)		
Age Group	**Typical**	**High-End**
<1	0.000010	0.00075
1- <2	0.000028	0.00058
2- <6	0.000028	0.00037
6- <16	0.000011	0.000019
16- <19	0.0000061	0.00013
19- <36	0.0000068	0.00012

Background: Dietary – Water

- Exposure concentrations for water were obtained from government databases:
  - EPA's National Drinking Water Contaminant Occurrence Database – for public water sources
  - U.S. Geological Survey (USGS) National Water Quality Assessment (NAWQA) program – for private well sources
- Used Lifeline™ Version 2.0 to model aggregate exposures to benzene from water

Ingestion, Inhalation and Dermal Exposure to Benzene from Water (mg/kg-d)		
Age Group	Typical	High-End
<1	0.000013	0.00020
1- <2	0.000029	0.00051
2- <6	0.000013	0.00023
6- <16	0.0000040	0.000040
16- <19	0.0000027	0.000029
19- <36	0.0000024	0.000021

Benzene in Soft Drinks

- Examined FDA Market Basket Surveys for benzene exposure from cola, diet cola, and fruit-flavored soft drinks
- Benzene is believed to be formed as a reaction by product between ascorbic acid and sodium benzoate (preservative), in combination with elevated temperatures

Detection Frequency 1996 - 2001 (24 Market Basket Surveys):

- Diet cola = 20 of 24
- Fruit-flavored carbonated drink = 9 of 24
- Cola = 5 of 24

- Benzene Concentrations:
  - Diet Cola>Cola>Fruit-flavored carbonated drinks

Benzene in Diet Cola from FDA 2001 Market Basket Study	
Quarter	Concentration (ug/L)
1	30
2	4
3	11
4	5

Benzene Exposure from Diet Colas

(based on FDA 2001 Market Basket surveys)

Age Group	Average Daily Ingestion Rate of Soft Drinks (EPA, 2002) (g/day)	Typical (mg/kg-d)[1]	High-End (mg/kg-d)[2]
<1	0.06	$1.3x10^{-7}$	$2.3x10^{-7}$
1 - <2	4	$5.0x10^{-6}$	$8.9x10^{-6}$
2 - 6 yr	9	$8.6x10^{-6}$	$1.5x10^{-5}$
6 - <16	27	$8.6x10^{-6}$	$1.5x10^{-5}$
19 - <36 female	117 (1/3 can)	$2.9x10^{-5}$	$5.2x10^{-5}$
19 - <36 male	80 (1/4 can)	$1.6x10^{-5}$	$2.9x10^{-5}$

[1] Typical is for benzene concentration using mean 2001 concentration of 15 ug/L
[2] High End is for benzene concentration using 95th % 2001 concentration of 27.6 ug/L

For children less than 6 yr, the dose is less than that of drinking water. For children older than 6 and adults, the dose is similar to that of drinking water.

Most Recent FDA Analysis of Benzene in Soft Drinks

- Recent beverage survey by FDA's Center for Food Safety and Applied Nutrition (CFSAN) included 100 soft drinks and beverage samples.
- Most (91%) samples/products contained <5 ppb benzene; the majority were non-detect or <1 ppb.
- Many products have been reformulated since the 1990s to reduce the potential for benzene formation

Source: FDA 2006

- 9 samples (4 products) contained benzene > 5ppb (Benzene MCL)
  - Safeway Select Diet Orange (3 of 4 lots)
    - 10.7 – 79.2 ppb
  - AquaCal Strawberry Flavored Water (2 of 3 lots, not reformulated)
    - 9.2 – 23.4 ppb
  - Crystal Light Sunrise Classic Orange (2 of 4 lots, not reformulated)
    - 73.9 – 87.9 ppb
  - Giant Light Cranberry Juice Cocktail (2 of 2 lots)
    - 5.4 – 10.7 ppb

Background: Human Milk

- Evaluated as a potential source of exposure for infants <1yr old.
- Used pharmacokinetic model by Fisher et al. (1997) to calculate benzene concentrations in human milk
- Evaluated occupationally and non-occupationally exposed mother
- Compared results with measured values from Fabietti et al. (2004) and found to be similar

Scenario	Ingestion of Benzene from Human Milk (mg/kg-day)
Urban, typical	0.0000023
Urban, high-end	0.000016
Occupational, typical	0.00019
Occupational, high-end	0.00068

Source Specific: Gasoline

- Evaluated in-vehicle and refueling exposures
- Used exposure concentrations from the published literature (adjusted refueling values)
- Exposure concentrations during refueling significantly higher than in-vehicle, but exposure duration for refueling is very short (e.g., 3 minutes)

Scenario	Typical Benzene Exposure in µg/m3 (ppb)	High-End Benzene Exposure in µg/m3 (ppb)
In-Vehicle	5.7* (1.8)	5.7 (1.8)
Refueling	450 (140)	1,600 (500)

*Assumed because no data for typical

Gasoline Normalization Factor

- Adjusted historical benzene air concentrations during refueling to account for:
  - Current day fleet improvements
  - Benzene content in reformulated gasoline
- Used EPA Mobile 6.2 model to estimate change in benzene emission rates between study year fleet and benzene content in gasoline vs. 2003 fleet and benzene content
- Normalization Factor ranged from 1.3 to 5.5

Source Specific: Consumer Products

- Reviewed consumer product survey (Sack and Steele, 1991) that identified the following categories may contain benzene >0.1% by weight :
  - Spot remover
  - Carburetor and choke cleaner
  - Silicone lubricant
  - Gasket adhesives/remover
- Verified current formulations of the products identified by Sack and found that either benzene not listed (assumed to be <0.1%) or noted to be <0.1%.
- Therefore, exposures from this source were considered *de minimis* and not quantified.

Trace Benzene in Petroleum Based Solvents

Solvent	Measured Benzene Concentrations (ACC, 2006)
Hexanes	<0.5 - <10 (ppmv)
VM&P Naphtha	<0.5 – <10 (ppmv)
Stoddard Solvents:	
Unspecified	<0.4 - <50 (ppmv)
Type A (8-22% aromatic)	<0.4 - <50 (ppmv)
Type B (<8% aromatic)	<20 (ppmv)
Type C (<2% aromatic)	<1 (ppmv)
Mineral Spirits (type not specified)	<0.4 - <50 (ppmv)

Source Specific: Tobacco Smoke

- Evaluated environmental tobacco smoke (ETS) and mainstream smoke
- Published literature used to determine benzene emission rate
- ETS: Modeled benzene indoor air concentration due to ETS using EPA indoor air model (i.e., MCCEM)
- Mainstream: Calculated benzene cigarette emission rate (µg/cigarette)

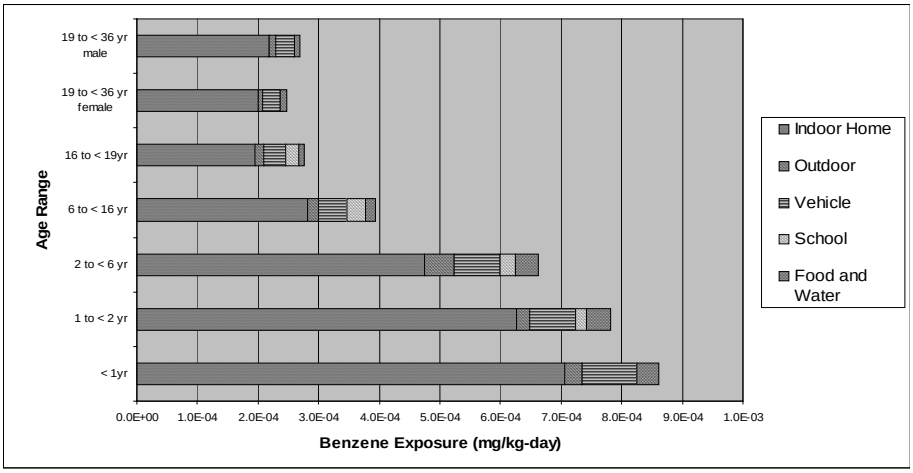
- Findings:
  - Benzene concentration from ETS adds about 1 µg/m3 to the indoor air. Benzene exposures from ETS in the home ranged from 0.00007 mg/kg-day to 0.0001 mg/kg day
  - Benzene exposure from mainstream tobacco smoke ranged from 0.004 mg/kg-day to 0.009 mg/kg-day

Source Specific: Occupational

- Evaluated the published literature (chemical mfg, woodland fire fighter, etc) and consortium member industrial hygiene data
- Consortium data (from petrochemical mfg and distribution) from 1995 – 2000 was used for typical and high-end
- Used exposure data to calculate human milk concentrations

Scenario	Benzene Exposure Concentration 8-hr TWA in mg/m3 (ppm)
Typical	0.35 (0.11)
High-End	1.2 (0.39)

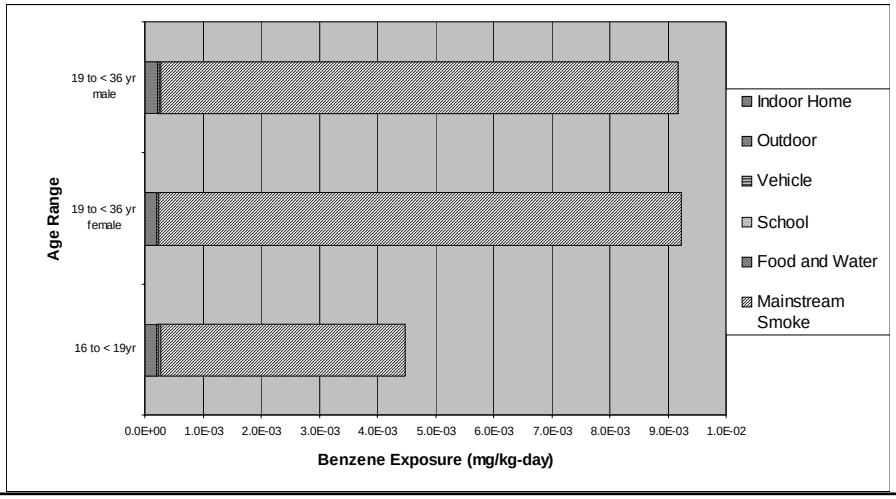
Contribution of Various Sources to Typical Chronic Exposures *(expressed as annual average daily dose)*



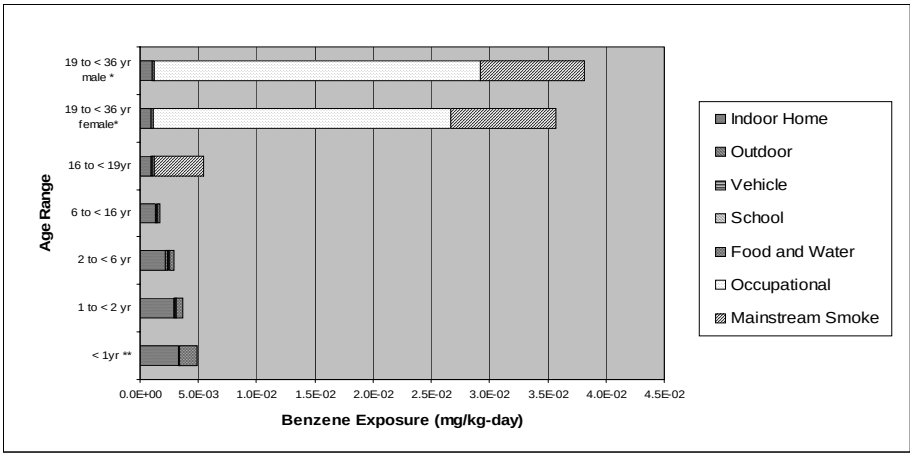
* Representative of a nursing infant (<1 yr) with a non-occupationally exposed mother.

Comparison of Exposure from Mainstream Smoke to Typical Background Sources

(expressed as annual average daily dose)



Contribution of Various Sources to High-end Chronic Exposures *(expressed as annual average daily dose)*



* Includes high-end occupational exposure

** Representative of a nursing infant (<1 yr) of a high-end occupationally exposed mother

Conclusions

- Sources of Exposure
  - Robust data set exists for of all major sources of benzene exposure to children and prospective parents
  - Exposure concentration data are adequate to quantify typical and high end exposures via inhalation, ingestion and dermal absorption
  - Exposure scenarios included all typical background sources of exposure (outdoor ambient air, indoor air, food, and water) and also characterized exposure from various specific sources and activities (in-vehicle, refueling, occupational and smoking).
- No unique exposure scenarios for children were identified other than the nursing infant.

Benzene VCCEP Risk Assessment

June 16, 2006
TERA, Cincinnati, Ohio

Presenter: Sean Hays
Summit Toxicology, L.L.P.

Overview

- Hazard
- Exposure
- Children's Potential Relative Sensitivities
- Dose-Response
- Findings from Risk Assessment

Hazard

- Our understanding of benzene hazards is mostly based on observations in workers.
- Cytopenias:
  - IRIS: deemed to be the most sensitive endpoint
  - Observed after high (>5 – 10 ppm) historical occupational exposures
- Reproductive/developmental:
  - Humans - No consistent findings
  - Animals – Occurs at exposures greater than those that cause cytopenias
- AML:
  - The only consistently observed malignancy
  - Observed in high historical occupational exposures

Exposure

- Can be aggregated across all routes and sources (based on absorbed dose):
  - No route of entry effects of consequence
  - Approach adopted by USEPA in IRIS to develop the RfD for benzene

Risk Assessment Approach

- Non-cancer
  - Hazard quotient (HQ)
  - Margin of safety (MOS)
- Cancer
  - Default EPA approach (cancer slope factor)
  - Margin of safety (MOS)
- *Key issue: Relative sensitivity of children compared to adults for cytopenias and AML*

Children's Sensitivity to Chemically-Induced Cytopenias: The MTD Study

- National Cancer Institute sponsored studies evaluated the maximally tolerated dose of a variety of cytotoxic drugs in children and adults.
- Myelosuppression was the dose-limiting toxicity for:
  - 12 out of 16 tested drugs: Glaubiger et al. (1982)
  - 10 out of 17 tested drugs: Marsoni et al. (1985)
- In most cases, children were able to tolerate higher doses than adults:
  - 9 out of 12 tested drugs: Glaubiger et al. (1982)
  - 7 out of 10 tested drugs: Marsoni et al. (1985)
- Based on this analysis, there is also no apparent intrinsic sensitivity to chemically induced hematopoietic toxicity associated with a younger age.

Children's Sensitivity to AML

- No direct observational data on risk of leukemia in children following exposure to benzene exist.
- Therefore, data on occurrence of therapy related AML (t-AML/t-ANLL) was collected from the clinical and medical literature. These data were used to characterize the effects of age on chemically-induced leukemia risk (children vs. adults, children of different ages).
- Hypothesis:
  - t-AML/ANLL represents an appropriate surrogate for benzene-induced leukemia.

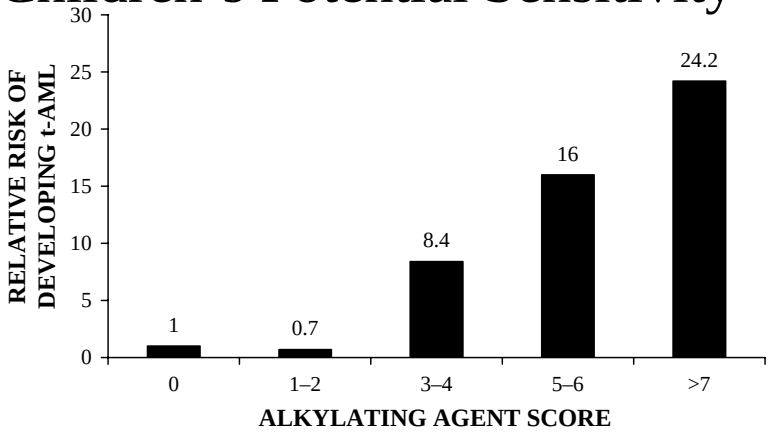
t-AML Following Treatment of Hodgkin's Disease (HD)

- HD occurs in both adults and children; substantial body of literature on t-AML development.
- HD generally treated in similar ways in adults and children:
  - Alkylating chemotherapy (MOPP) w or w/o radiation
    - MOPP: Mustarogen (nitrogen mustard), Oncovin (vincristine), Procarbazine, and Prednisolone
  - Doses similar on a surface area basis
  - Rarely use topoisomerase reactive drugs
  - Radiation does not seem to be a major confounding factor in these studies.

t-AML Following Treatment with Topoisomerase Inhibitors

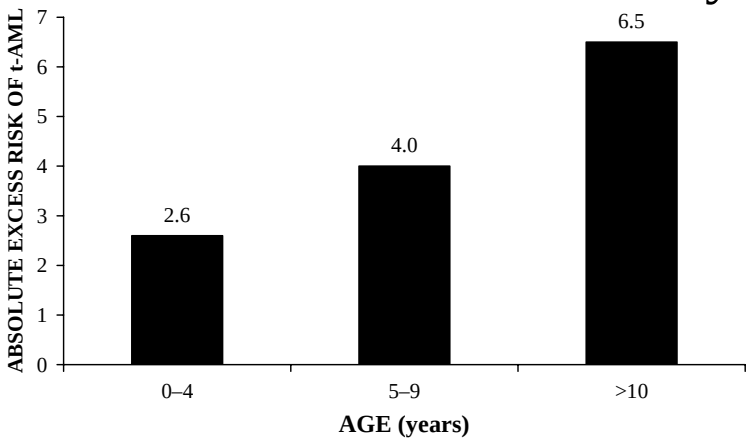
- Used to treat ALL.
- Smaller body of literature on risk of t-AML following topoisomerase inhibitor treatment.

Children's Potential Sensitivity



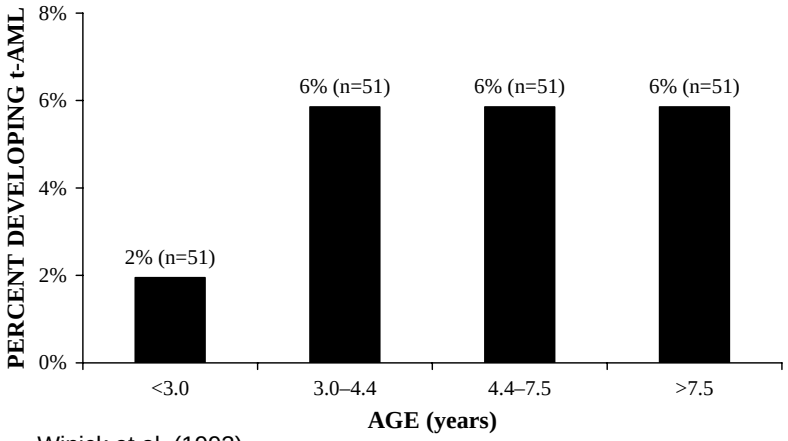
Tucker et al. (1987)

Children's Potential Sensitivity



Tucker et al. (1987)

Children's Potential Sensitivity



Winick et al. (1993)

Conclusions on Children's Sensitivity to t-AML Based on Clinical Literature

- No indication of differential relative risk for developing t-AML:
  - In children compared to adults
  - In younger children compared to older children or adolescents
  - Following chemotherapy with either alkylating agents or topoisomerase inhibitors (despite different morphological and cytogenetic characteristics)
- Studies were powerful enough to detect:
  - Clear age-dependence of risks of other types of treatment-related tumors
  - Clear dose-response relationships

Conclusions on Children's Sensitivity to t-AML (Cont'd)

- This analysis has shown:
  - Consistent findings with both alkylating agents and topoisomerase inhibitors
  - Dose-response
  - Age-related differential sensitivity
    - Elderly
    - Solid tumors
- *Pyatt et al. 2005 Chemical-Biological Interactions*
- *Pyatt et al. 2006 Journal of Toxicology and Environmental Health: Part B (accepted, pending revisions)*

Conclusion on Children's Sensitivity – Risk Assessment

- No need for extra child-specific safety factors for chemically-induced:
  - AML
  - Cytopenias

Dose – Response: Non-Cancer (USEPA's RfC/RfD)

- Rothman et al. (1996)
- Absolute Lymphocyte Count (ALC) was most sensitive endpoint
  - ALC statistically significantly decreased (but within the normal range)
  - Deemed by USEPA to not be a frank effect
- 44 workers and age matched controls
  - Median exposure duration: 6.3 yrs
  - Median TWA of exposed workers: 31 ppm; divided into 2 groups:
    - Median TWA for these groups: 13.6 and 91.9 ppm
  - Effects on ALC independent of exposure duration
  - Benchmark dose modeling:
    - BMCL = 7.2 ppm (using 1 SD as the BMR)
    - Adjusted Bench Mark Concentration Lower Limit (BMCL) for general population: 2.57 ppm
    - 5/7 days/week & 10/20 m^3/day

Alternative RfC & RfD

Uncertainty Factors	IRIS	Alternative 1	Alternative 2	Alternative 3	Rationale
Effect level extrapolation	3	3	3	3	
Intraspecies variability	10	3	3	3	A full factor of 10 is not supported by literature on child-specific sensitivity to cytopenias
Subchronic to chronic	3	3	1	1	No effect of duration of exposure found in Rothman
Database Deficiency	3	3	3	1	Cytopenias appear to be the most sensitive endpoint
Composite UF	*300*	*81*	*27*	*9*	
Resulting RfC (mg/m^3)	**0.027**	**0.10**	**0.30**	**0.91**	
Resulting RfD (mg/kg-d)	**0.004**	**0.01**	**0.03**	**0.1**	

Pliofilm Exposure - Response

Exposure Estimates	Cumulative Exposure (ppm-years)	Observed [a]	Expected	SMR	95% Confidence Interval
Rinsky (1987)	0.5	3	1.52	1.97	0.41-5.67
	>5-50	3	1.31	2.29	0.47-6.69
	>50-500	7	1.01	6.93[c]	2.78-14.28
	>500	1	0.05	20.00	0.51-111.4
Crump (1984)	0.5	1	1.14	0.88	0.02-4.89
	>5-50	4	1.23	3.25	0.88-8.33
	>50-500	6	1.23	4.87[b]	1.79-10.63
	>500	3	0.29	10.34[c]	2.13-30.21
Paustenbach (1992)	0.5	1	0.75	1.33	0.03-7.43
	>5-50	2	1.12	1.79	0.22-6.45
	>50-500	4	1.43	2.80	0.76-7.16
	>500	7	0.59	11.86[c]	4.76-24.44

From Paxton, M.B. *et al*, . 1994. Leukemia Risk Associated with Benzene Exposure in the Pliofilm Cohort: I. Mortality Update and Exposure Distribution. *Risk Analysis*, V14, N2, p 153. With Permission.

a – White male wetside workers: b – $p < 0.05$: c – $p < 0.01$

Cancer Slope Factors

- EPA derived CSFs based on:
  - Pliofilm cohort AML mortality (Rinsky et al., 1987)
  - Exposures: Crump and Allen (1984) and Paustenbach et al. (1992)
- Crump (1992; 1994) derived 96 unit cancer risk estimates with a range of:
  - 8.6×10^{-5} to 2.5×10^{-2} at 1 ppm (a range of 290)
- EPA chose the upper end of the range
  - 7.1×10^{-3} to 2.5×10^{-2} at 1 ppm (a range of 3.5)
  - Based on a policy decision to only accept linear extrapolation to low exposures

Cancer Slope Factors

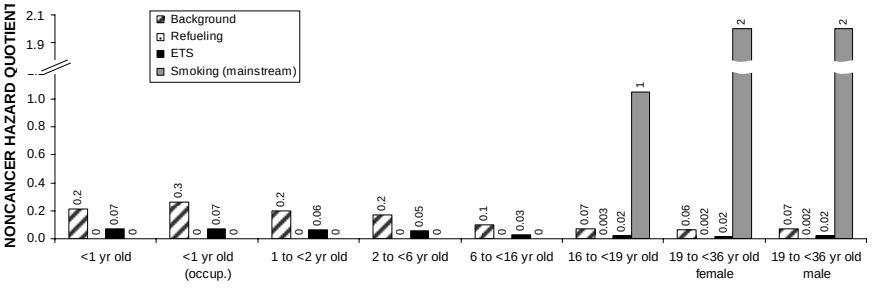
- Cancer Slope Factors $(mg/kg/day)^{-1}$ used in this VCCEP assessment
  - Upper-Bound Linear Model: 5.5×10^{-2}
  - Lower-Bound Linear Model: 1.5×10^{-2}
  - Lower Bound Nonlinear Model: 1.9×10^{-4}

Non-Linear Dose-Response

- Scientific literature supports a functional threshold for AML & cytopenias
- The European Union recently conducted a risk assessment for benzene
  - Employed a Margin of Safety approach using Points of Departure (PODs) for cancer and non-cancer effects
  - Non-cancer POD: 1 ppm
  - Cancer POD: 0.1 ppm

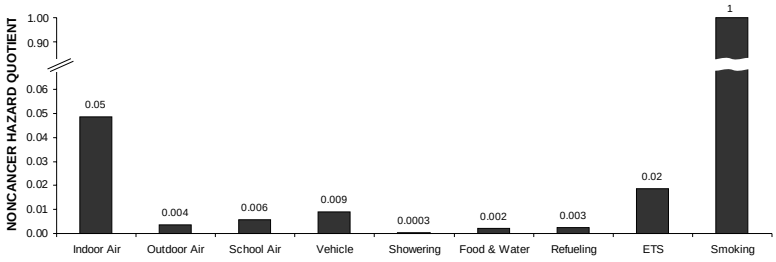
Risk Assessment Results

Risk Assessment Results: by Age and Source



Notes: Hazard quotients were calculated using the default IRIS reference dose.
Typical values were used for all pathways and outdoor air is urban.

Risk Assessment Results
Source-Specific
(16-19 year olds)

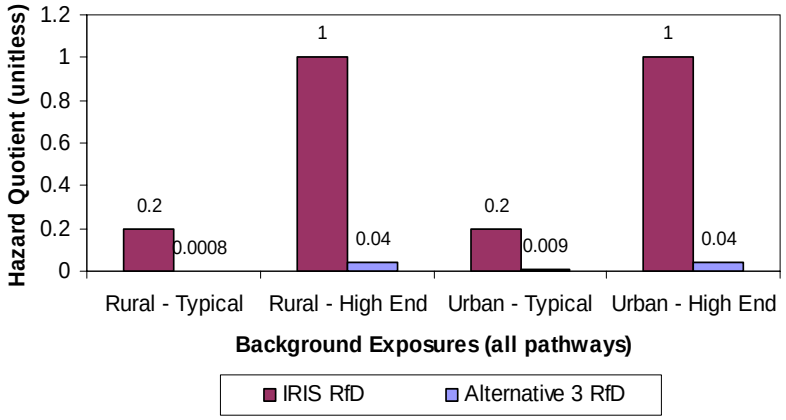


Source-specific hazard quotients were calculated using USEPA's IRIS RfD.

Alaska

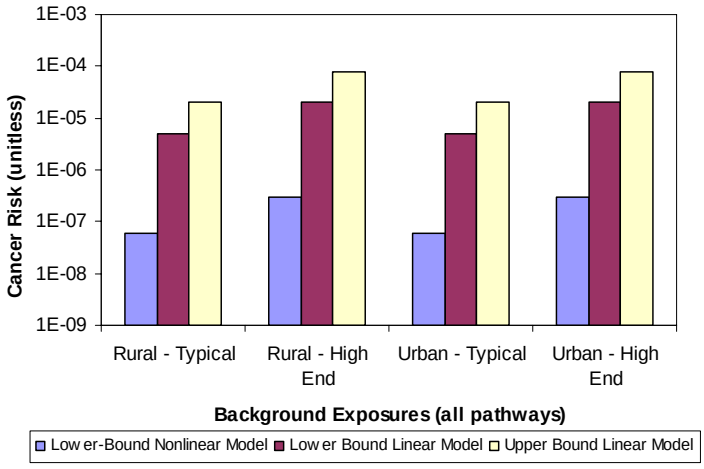
- Limited exposure data.
- Understanding of benzene concentrations in homes with attached garages has been an area of active research.
- Concentrations have declined over the past 10-20 years.
- Based on current levels of benzene in some Alaska homes:
  - Non-Cancer
    - HQ: 0.01 to 2 (based on range of RfDs and age categories)
    - MOS: 73 to 450 (based on age categories)
  - Cancer
    - EPA default approach: 4E-7 to 1E-4 (based on range of CSFs)
    - MOS: 24 to 25

Impact of Choice of Uncertainty Factors



Less than 1 year old – sum of all background pathways

Impact of Choice of Cancer Dose-Response Modeling



Risk Assessment Findings

- General population:
  - Mainstream cigarette smoke is largest source of benzene exposures and thus risks among general population.
- Children:
  - High end indoor air poses the greatest source of exposure and thus risks for children (particularly < 6 years of age).
  - Riding in cars and refueling do not contribute significantly to overall/aggregate exposures (due to shorter durations) and thus risks.

Risk Perspectives

- Concentrations of benzene have been declining in the environment over the past 25 years.
- The incidence of childhood leukemia (mostly ALL) has increased over the past 20-30 years; AML has remained largely unchanged.
- The incidence of leukemia and AML in Alaska (3.3 per 100,00: 1.7 – 5.9) does not appear to be any different than the lower 48 (2.8 per 100,000), despite having potentially significantly higher exposures to benzene.

Concluding Observations

- The available scientific evidence indicates that children should be no more sensitive to benzene-induced AML or cytopenias than adults
  - Therefore, an additional safety factor to protect children is unwarranted.
- Ranges of RfDs and CSFs provides:
  - Greater transparency
  - Insights into risks from general environmental exposures to benzene.

Concluding Observations

- The available scientific literature supports a functional threshold for benzene-induced cytopenias and AML.
- The MOS approach is appropriate for benzene and provides additional insights into risks for the general population.

Appendix E

Voluntary Children's Chemical Evaluation Program (VCCEP)
Peer Consultations on Benzene
June 15-16, 2006

Additional Details of Data Needs from One Panel Member

In the absence of a more complete data base on the mechanisms of benzene-induced bone marrow damage, the significance of exposure assessment and the accuracy of risk assessment are somewhat limited. With respect to research on the toxicology of benzene, I have thoughts about some specific areas that need to be completed before we can have a better feel for the potential effects of benzene on children.

The needs listed below reflect additional studies on the mechanism of benzene-induced bone marrow depression leading to aplastic anemia and benzene-induced myelodysplasia leading to acute myelogenous leukemia. 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, i.e., some function of dose X time of exposure.

1. Determine the best animal surrogates for studies of either marrow depression or leukemogenesis. The Tg.AC mouse is the only animal which yet examined in which a granulocytic leukemia can be induced with benzene, but application through skin was the route. A model better related to human inhalation exposure is needed.

2. Effects on animals *in utero* aimed at either the embryonic stage or the fetal stage of development over a wide range of doses is needed. A number of specific issues have not been examined. For example, in utero the liver serves as a significant hematopoietic organ. Benzene is metabolized in liver and reactive metabolites may have direct access to developing hematopoietic cells in the liver. The effects of benzene and its metabolites on blood cell production in the liver, the impact of exposure on signal transduction pathways in the developing organism, the metabolism of benzene and covalent binding to macromolecules in the bone marrow surrogate organ should examined. The latter issue should not be restricted to nucleic acids, but should consider important proteins as well. For example, reactive benzene metabolites bind to hemoglobin in adults, but it has not been shown to impair tissue oxygenation. However, adequacy of oxygenation of the fetus might be examined because it is not known to what degree reactive benzene metabolites bind to fetal hemoglobin or the impact of such binding on development

3. It will be important to expose animals *in utero* and to examine the post natal effects of benzene as well. Thus, early examination looking for signs of childhood leukemia will be important, as will leukemia that may develop later in life. For example, is there any indication of chromosomal abnormalities after *in utero* exposure.

4. Signal transduction pathways, as mentioned above should be carefully examined. Recent evidence points to effects of vHarvey ras, c-Myc and others as having a role to play in leukemogenesis and the impact of benzene metabolites should be characterized.

5. The VCCEP document is largely a review of the benzene literature. The two major diseases which we attribute to benzene are bone marrow depression leading to aplastic anemia and AML. Analysis of the hematological literature relating to these diseases is a daunting task. Nevertheless, failure to examine current thinking about either of these disease entities can inhibit the process of deciding upon needed future research on benzene.

    a. For example, within the bone marrow, the hematopoietic microenvironment, i.e., the stroma plays a key role in supporting differentiation and proliferation of bone marrow cells. Failure of the stroma may result in various cytopenias and eventually aplastic anemia. There have been some suggestions that the primary effect of benzene in aplastic anemia is on the stroma rather than on the developing cells. The susceptibility of children to effects on the stroma has yet to be explored.

    b. The development of myelodysplasia appears to be an important intermediary stage in the development of AML in adults. Dysplasia involves a number of described alterations in bone marrow morphology, and is frequently accompanied by a variety of cytopenias, as well. Indeed, the claim that AML results only after the bone marrow displays various cytopenias may be a reflection of myelodysplasia. A constant observation in leukemias in general, in myelodysplasia, and in benzene poisoning is the appearance of chromosome aberrations of various types. There are distinct parallels between *de novo* AML, AML induced by specific types of cancer chemotherapy, and benzene-induced AML, in that aberrations occur primarily, but not exclusively, in chromosomes 5 and 7. Examination of chromosomal damage at various ages following benzene exposure is needed.

    c. An area in need of examination is the effect of benzene on the immune system. It is clear that people who die of benzene poisoning, die of infections because of the immune system is not functional. Effects of benzene on the immune system of children need to be examined.

    d. The three areas suggested here enforce the need to find reliable animal models for the study of these effects.

6. Finally, we find ourselves in the midst of the genomic revolution. Research on almost every physiological function is aimed at uncovering the genomic basis of physiology. Side by side we are beginning to examine the effects of genomic alterations on pathological outcomes of exposure to chemicals. Some work has begun with respect to benzene, but it is a wide open field. Examination of genomic damage, leading to proteomic changes, and ultimately the impact on cell physiology in the bone marrow, is an absolute requirement if we are to understand benzene-induced hematopoietic disturbances both in children and adults.