Appendix A

List of Attendees

VCCEP Peer Consultation for Toluene
Northern Kentucky University, METS Center
November 7-8, 2006
List of Attendees

Dr. Katherine Anitole*
U.S. EPA, Office of Pollution, Prevention and Toxics

Ms. Lesa Aylward
Summit Toxicology, LLP

Dr. John Bukowski
WordsWorld Consulting

Ms. Patsy Clegg
Shell Chemical Company

Ms. Carol Fairbrother*
ExxonMobil Chemical Company

Dr. Ralph Gingell
Shell Health Services, SHLOIL-SHS

Mr. Sean Hays
Summit Toxicology, LLP

Dr. Colette Hodes*
U.S. EPA

Mr. Andrew Jaques
American Chemistry Council

Dr. Sophie Jia*
CHEVRON PHILLIPS Chemical Company LP

Dr. Janet E. Kester*
NewFields

Dr. Lawrence K. Low*
ExxonMobil Biomedical Sciences, Inc.

Ms. Julie M. Panko
ChemRisk

Mr. Craig M. Parker*
Marathon Petroleum Company

Ms. Andrea Pfahles-Hutchens*
U.S. EPA

Dr. Ceinwen A Schreiner
C&C, Consulting in Toxicology for American Chemistry Council

Dr. Jennifer Seed*
U.S. EPA

Mrs. Deborah P. Sherer*
US EPA Office of Pollution Prevention and Toxics

Dr. Lisa M. Sweeney*
The Sapphire Group

Mr. Mark Wine*
Kirkland & Ellis LLP

Appendix B

Meeting Materials

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

Table of Contents

Agenda
VCCEP Peer Consultation for Toluene
Northern Kentucky University, METS Center
November 7-8, 2006

Tuesday, November 7, 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: Animal Toxicity – Dr. Ceinwen Schreiner, C&C Consulting
Human Health – Dr. John Bukowski, WordsWorld 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

Wednesday, November 8, 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

This document provides background information on the VCCEP pilot program and the peer consultation. It is presented in two parts: General Background on VCCEP and Overview of How *TERA* Organizes and Conducts VCCEP Peer Consultation Meetings. The expectations for panelists and their responsibilities before, during, and after the panel meeting also are briefly discussed. Please contact Dan Briggs at briggs@tera.org if you have questions or desire additional information.

General Background on VCCEP

In the December 26, 2000 Federal Register, http://www.epa.gov/fedrgstr/EPA-TOX/2000/December/Day-26/t32767.htm, EPA announced the Voluntary Children's Chemical Evaluation Program (VCCEP) pilot program. This program is intended to provide data to enable the public to understand the potential health risks to children associated with certain chemical exposures. The key questions of the program are whether the existing data on a given chemical are sufficient to adequately characterize the potential hazards, exposures, and risks to children and prospective parents, and, if not, what additional data are necessary.

The VCCEP pilot program uses a tiered testing approach. For toxicity (health effects) data, specific types of studies have been assigned to one of three tiers. For exposure data, the types of studies required are less specific, but the depth of exposure information increases with each tier.

EPA asked companies which manufacture and/or import 23 chemicals found in human tissues and the environment to volunteer to sponsor an evaluation of their chemicals in a pilot of the VCCEP. Sponsorship requires the companies to collect or develop health effects and exposure information on their chemicals and then to integrate that information in a risk assessment and a data needs assessment. If data needs are identified through this process, the sponsor will choose whether or not to volunteer for any additional data generation or testing and whether to provide additional assessments. Thirty-five companies and ten consortia responded and volunteered to sponsor 20 chemicals in Tier 1.

TERA was awarded a Cooperative Agreement by EPA to design, develop, and manage a peer consultation process that would serve as a public scientific forum. One of the activities undertaken by *TERA* under this agreement is the VCCEP plot program. *TERA's* primary role in this program is to ensure it is a rigorous, science-based process for reviewing VCCEP assessments. Stakeholders should recognize the process as impartial and of significant technical merit and value. *TERA's* role in managing the peer consultation is undertaken primarily at the request of and for the benefit of non-federal VCCEP stakeholders, particularly the sponsors of VCCEP chemicals.

Overview of How *TERA* Organizes and Conducts VCCEP Peer Consultation Meetings

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. For the VCCEP pilot program, *TERA*'s responsibilities include identifying and recruiting scientists with relevant expertise to comprise a peer consultation panel, identifying and managing conflict of interest and bias issues of the panel candidates, organizing and conducting the peer consultation panel meetings, and drafting and finalizing the meeting reports.

The panel meeting provides a science-based peer consultation on the data needs for the chemical, utilizing not only the assessment submitted by the sponsor, but also the expertise and knowledge of the panel. Members of the peer consultation panels are selected by *TERA* based on their expertise in scientific disciplines relevant to the chemicals, test methodologies, and risk assessment issues that will be discussed. Nominations for panel members are welcomed from all interested parties. *TERA* selects the panel members from among those nominated and also from among other qualified experts whom *TERA* independently identifies.

Each panel candidate discloses information regarding potential conflicts of interest and biases. *TERA* evaluates these disclosures in selecting the panel members following procedures in accordance with the U.S. Office of Management and Budget, the National Academy of Sciences, and the U.S. EPA. These procedures are described in more detail at http://www.tera.org/peer/COI.html.

Panel members also are selected to bring a wide range of views and perspectives to the peer consultations, reflecting the interest in VCCEP by a wide range of stakeholders. The panel does not attempt to reach consensus positions; rather, the individual opinions of each of the members are noted.

Members of the public are invited to attend the peer consultation meetings, and they are invited to provide brief oral and written technical comments on the assessment document for the panel's consideration. Recent panel meetings have been made available to pre-registered, off-site observers via real-time web casts.

TERA reviews the sponsor's VCCEP chemical assessment document and develops a panel charge to guide the panel in its discussions during the meeting. The panel charge focuses the meeting discussions by presenting specific items for the panel to address. General questions regarding completeness and interpretation of data are included, as well as more specific questions relevant to the hazard, exposure, or risk characterization of the specific VCCEP chemical being evaluated. The charge includes questions regarding data gaps and data needs and asks panelists to identify data needs and their rationale for them.

TERA is responsible for all meeting preparations including travel and logistics, announcements, distribution of the review materials, and assisting the panel. VCCEP peer consultation meetings generally follow a standard *TERA* process, beginning with a close examination of the sponsor's report and supporting documentation by the panel prior to the meeting.

At the beginning of the meeting, panelist disclosures regarding potential conflict of interest and bias issues are presented and discussed. *TERA* believes transparency in these matters is important and therefore discusses these openly at the meeting, allowing panel members to question one another. These disclosures are also part of the public record through inclusion in the meeting report. The Chair then discusses the ground rules for the meeting. Ground rules generally include the following items:

- Chair will call upon panel members in turn and will interrupt discussion if he thinks the topic is drifting. He will not call upon observers. Observers can talk to the Chair or to *TERA* staff during a break in the meeting if they wish to schedule a time to comment.

- If a panelist states a part of the assessment unacceptable, he or she will be asked to explicitly state what additional work would be needed to make it acceptable. The Chair may ask the panelist to work with the sponsor to resolve the issues during the breaks.

- Panel members will have provided premeeting comments before the meeting. These comments are informal and not part of the meeting record. They are initial thoughts that were shared with the sponsor and other panel members to help identify issues and new data. Panel members must raise items in their premeeting comments during the meeting in order for them to be included in the meeting record.

The meeting discussions are limited to panel members. One or two authors or sponsor representatives sit at the table to answer panel questions. These representatives are allowed to ask the panel members clarifying questions as needed. In order to avoid the appearance of undue influence on the panel, all parties are asked to refrain from discussing issues related to this review with panel members prior to the meeting or during the breaks unless a panel member initiates the discussion. Panel members are asked to summarize any substantive conversations for the rest of the panel and audience when the meeting reconvenes after the break.

The discussion period begins with the authors or sponsors making short presentations summarizing their report and possibly also addressing issues raised by the panelists in their premeeting comments. These presentations highlight salient issues and give the panel the opportunity to ask clarifying questions. The Chair then leads the panel in discussions, using the items in the panel charge. Individual panelists will be asked to share their opinions and defend them with scientific data and analysis.

TERA scientists take notes of the meeting discussions and prepare a draft meeting report summarizing the panelists' discussions, conclusions and recommendations. This report is not a transcript of the meeting but a summary of the key discussions and issues. Panel members are listed, but their individual comments are not attributed to them by name. The draft report is reviewed by the panel. The sponsors also are allowed to review the draft report, but they must limit their comments to matters of clarity and completeness regarding their presentations and statements made at the meeting. The meeting report includes copies of the sponsor presentation slides, a list of attendees, panel biographical sketches and COI/bias disclosures, and public comments. When finalized, the meeting reports are made available to the public on *TERA*'s Peer Review and Consultation website (http://www.tera.org/peer/welcome.htm).

Panelist Biographical Sketches and Conflict of Interest Disclosures

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 Toluene 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. For toluene, *TERA* has evaluated various aspects of toluene's toxicity in a number of limited projects for several sponsors, including U.S. EPA (In a project of EPA Office of Water, *TERA* is currently evaluating toluene toxicity data to determine if updating of RfD or cancer assessment is needed and whether development of a RfD for developmental toxicity is appropriate), U.S. Army (past), and a private company (past). None of this work was related to the VCCEP assessment, nor was it work done for any VCCEP sponsor of toluene.

The purpose of this VCCEP Toluene 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.

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. EPA 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 the past Secretary for the Society for Risk Analysis, and has also served as presidents 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 well over 100 government risk assessment documents, and has made over 100 invited presentations.

Dr. Dourson is a core panel member. He was selected for the core panel because of his expertise in toxicology, risk assessment, and derivation of non-cancer risk values.

Disclosure

Dr. Dourson is Director of *TERA*. He has chaired or participated in over 100 scientific peer review meetings funded by numerous organizations including, U.S. EPA, the American Chemistry Council (ACC) and private companies, including several of the VCCEP toluene sponsors. None of these review meetings was specifically on toluene, except for those of the RfD/RfC Work Group of EPA. 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 toluene. As an employee of *TERA*, Dr. Dourson also has

contributed to non-toluene related research and development activities sponsored by ACC, DuPont, and BP; as well as contributed to some *TERA* projects that involved toluene in some fashion.

TERA has determined that Dr Dourson has no conflicts of interest. His previous activities with ACC and VCCEP sponsors are being disclosed to assure transparency. *TERA* does not believe these activities will impair Dr. Dourson's scientific objectivity as a VCCEP toluene panel member.

Dr. Michael Bates

Dr Michael Bates is Adjunct Professor of Epidemiology in the Division of Environmental Health Sciences of the School of Public Health, at the University of California, Berkeley. In this position he carries out teaching in epidemiology and epidemiologic research in a number of areas. These research areas include health effects of chronic exposure to low levels of arsenic in drinking water, effects of indoor (cooking) smoke exposure in India and Nepal, and chronic health effects of low-level hydrogen sulfide exposure in the Rotorua geothermal area of New Zealand.

Prior to taking up his present position at Berkeley, Dr Bates worked as an environmental and occupational epidemiologist in the Institute of Environmental Science and Research (ESR) in New Zealand. Research carried out in this position included investigation of cancer risks in firefighters, measurement of organochlorines in the serum and breast milk of the New Zealand population, investigations of sources of lead exposure in children, investigation of hydrogen sulfide effects, and a retrospective cohort study examining the question of whether dental amalgam fillings (containing mercury) were associated with health effects. The work also involved conducting acute disease outbreak investigations and managing several national surveillance systems, including the New Zealand notifiable disease surveillance system.

The early part of Dr Bates' career was in toxicology. He obtained a B.Sc. in chemistry from the University of Canterbury, New Zealand, and an M.Sc. in toxicology from the University of Surrey, England. Until 1987 he worked as a regulatory toxicologist in the New Zealand Department of Health, directing the Toxicology Section from 1980. The section was responsible for toxicological assessment of pesticides, industrial chemicals and household products. Deciding in the mid-'80s to shift his career focus towards environmental epidemiology, Dr Bates obtained an M.P.H. in environmental health sciences and a Ph.D. in Epidemiology from the University of California, Berkeley. The focus of his doctoral dissertation research was carcinogenic effects of arsenic in drinking water. This work produced some of the earliest and most widely cited papers in this research area.

Following his Ph.D., Dr Bates worked as an epidemiologist at the University of Bielefeld, Germany, and then at ESR in New Zealand. In his career as an epidemiologist he has conducted epidemiologic research into a wide variety of topics and authored or co-authored over 100 scientific articles and reports. He has served on various scientific advisory panels, including the U.S. EPA's Scientific Advisory Panel on risks to children from arsenic-treated timber, and serves as a peer reviewer for numerous journals, including the *American Journal of Epidemiology*, the *International Journal of Epidemiology*, and *JAMA*.

Dr. Bates is an *ad hoc* panel member. He was selected for the toluene panel for his expertise in environmental and occupational epidemiology, as well as in toxicology.

Disclosure

None

TERA has determined that Dr Bates has no conflicts of interests.

Dr. William Boyes

Dr. William (Will) Boyes is an Environmental Health Scientist in the Neurophysiological Toxicology Branch, Neurotoxicology Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development of the U.S. EPA located in Research Triangle Park, North Carolina. Dr. Boyes served for 2 years as the Acting Director of the Neurotoxicology Division and for 13 years as the Chief of the Neurophysiological Toxicology Branch. He also served on a detail assignment to the EPA Office of Air Quality Planning and Standards. Dr. Boyes is engaged currently in a research program to develop exposure dose-response-models for the neurotoxic effects of exposure to volatile organic compounds. The goal of this collaborative program is to predict target tissue dose levels using physiologically-based pharmacokinetic models, and then link those dose levels to measures of neurotoxicity, in particular focusing on changes in neurophysiology that are indicative of impaired visual function.

Dr. Boyes received B.A. and M.A. degrees in physiological psychology from New Mexico State University, and in 1981 a Ph.D. in Environmental Health from the University of Cincinnati. He served as a National Research Council Research Associate for two years at the Neurotoxicology Division of EPA before joining EPA full time.

Dr. Boyes has published over 60 articles in the peer-reviewed scientific literature and over 20 book chapters and monographs dealing with various aspects of neurotoxicity. He has also contributed to numerous EPA publications and documents including EPA Neurotoxicity Testing Guidelines, EPA Neurotoxicity Risk Assessment Guidelines, The Office of Research and Development Air Toxics Research Strategy and the National Health and Environmental Effects Research Laboratory Air Toxics Research Implementation Plan. He has been a reviewer or contributor to several assessments of specific compounds published on the EPA Integrated Risk and Information System (IRIS) including that for toluene.

Dr. Boyes is currently the President Elect of the International Neurotoxicology Association. He is also a member of the Society of Toxicology, the Society for Risk Analysis and the Association for Research in Vision and Ophthalmology. He was an author of papers voted as one the “top ten” papers of 2003 and the “best paper” of 2005 in developing the scientific basis of risk assessment by the Specialty Section on Risk Assessment of the Society of Toxicology.

Dr. Boyes is an *ad hoc* panel member. He was selected for the toluene panel because of his experience in neurotoxicology and risk assessment and his work with neurotoxic effects of exposure to volatile organic compounds. Dr. Boyes’ recent publications include reports on extrapolating animal toxicity data on organic solvents to public health (*Neurotoxicology, 2006*) and acute behavioral effects of toluene in humans *(Risk Anal., 2005).*

Disclosure

Dr. Boyes is employed by the U.S. EPA, which has taken public positions on the VCCEP pilot chemicals, including toluene. The comments that Dr. Boyes makes during this meeting are his personal opinions, and his opinions should not be construed to represent the opinions of the U.S. EPA.

TERA has determined that Dr Boyes has no conflicts of interest.

Dr. Gary Burleson

Dr. Burleson is President and CEO at BRT-Burleson Research Technologies, Inc., a contract research organization (CRO) in Morrisville, North Carolina. BRT provides contract laboratory services to clients from the pharmaceutical, biotechnology, chemical manufacturing, and health care industries with proof-of-concept, pre-clinical efficacy, clinical trial immunoassay analyses, host resistance and infectious disease models in mice and rats, immunogenicity, and immunotoxicology studies. He has scientific expertise in the following broad areas: Immunotoxicology, Microbiology, Immunology, Virology, Clinical Microbiology, Viral Pathology, Pulmonary Immunology, Tumor Metastasis, Immunomodulation, Inflammation, Hypersensitivity, and Computer Disease Modeling.

Dr. Burleson received his Ph.D. in Viral Immunology from the Medical College of Wisconsin with post doctoral training at the University of Notre Dame. He has professional experience in academia, clinical, contract research, government research and the pharmaceutical industry. This experience includes academic appointments and affiliations at the University of Notre Dame and North Carolina State University; clinical experience at Milwaukee County General Hospital; contract research organization experience, government regulatory experience at the U.S. EPA; and pharmaceutical experience in drug discovery at the Procter & Gamble Company. He is a member of the Scientific Advisory Panel (FIFRA SAP) of the US EPA, and a member of the Editorial Board, Journal of Immunotoxicology. He was the organizer of a continuing education course entitled "Immunotoxicology," for 19th Annual Symposium of the Society of Toxicologic Pathologists at the Wigwam Resort in Phoenix AZ in 2000, and a Faculty Member at the 7th International Course on the Safety Assessment of Medicines - Basic and Regulatory Aspects, in 2000 in White Plains, NY. He has served as an NIH reviewer. He served as a member of the Editorial Board for Fundamental and Applied Toxicology and was a member of the Steering Committee for four years and President of the Immunotoxicology Discussion Group from 1992-1993.

Dr. Burleson participated in the preparation of a book entitled "Biologic Markers in Immunotoxicology" by the Committee on Biologic Markers, National Research Council, National Academy of Sciences. He was the Senior Editor for "Methods in Immunotoxicology, Volumes 1 and 2, 1995. He received the 2002 Alice Hamilton Award for Excellence in Occupational Safety and Health, Biological Science Category, for leadership through science in publishing the report "Association of TNFα and IL-1 gene polymorphisms with silicosis," in Toxicology and Applied Pharmacology 172:75-82 (2001).

Dr. Burleson is an *ad hoc* panel member. He was selected for the toluene panel because of his expertise in immunotoxicology and pulmonary immune function assays, as well as his experience in immunopharmacology investigations.

Disclosure

None

TERA has determined that Dr. Burleson has no conflicts of interest.

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). Dr. DeSesso is published extensively in the above areas of expertise, with publications both public and private numbering well over 100.

Dr. DeSesso is a core panel member. He was selected for the core panel because of his experience in reproductive and developmental toxicity, in teratology, and in risk assessment.

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-toluene chemicals in 2001. Mitretek Systems received payment for these services. Also in 2001, as an employee of Mitretek Systems, he co-authored a report that assessed the

developmental and reproductive toxicity data for two additives to a proposed new lubricant manufactured by one or more of the sponsors.

TERA has determined that Dr. DeSesso has no conflicts of interest. 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 toluene panel member.

Dr. Jeffrey Fisher

Dr. Fisher is a Professor 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 nonchlorinated 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 100 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.

Dr. Fisher is an *ad hoc* panel member. He was selected for the toluene panel because of his expertise in PBPK modeling in animals and in humans, as well as his experience in toxicology, metabolism, and risk assessment.

Disclosure

None

TERA has determined that Dr Fisher has no conflicts of interest.

Dr. Pertti (Bert) Hakkinen

Dr. Pertti (Bert) Hakkinen is a Principal of the Gradient Corporation, and leads its Product Safety practice. Formerly, he was on the staff of the European Commission at the EC's Joint Research Centre in the Physical and Chemical Exposure Unit of the Institute for Health and Consumer Protection. While at the EC, he helped 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. Also, Dr. Hakkinen was involved in an in-home exposure study of toluene while employed by P&G (results published in J. Expos. Anal. Environ. Epidemiol. 4: 443-456, 1994).

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 latest edition (2005) 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.

Dr. Hakkinen is a core panel member. He was selected for the core panel because of his experience in evaluating chemical exposures, especially to consumer product ingredients, and also because of his experience in toxicology and risk assessment.

Disclosure

Dr. Hakkinen chaired Exposure Assessment Task Groups and Panels of the American Chemistry Council (ACC) in 2001 and earlier. The ACC has sponsored various projects performed by Gradient, Dr. Hakkinen's current employer; however, none of that work focused on toluene. Gradient has had projects

of varying nature in past years with BP, Chevron Phillips Chemical LP, E.I. du Pont de Nemours & Company, and ExxonMobil Chemical (and/or their predecessor companies). These projects were or are unrelated to toluene and the VCCEP.

TERA has determined that Dr Hakkinen has no conflicts of interest. His chairing of ACC task groups and panels in 2001, together with Gradient's work for ACC and toluene sponsors before Dr. Hakkinen joined Gradient, are being disclosed to assure transparency. *TERA* does not believe Dr. Hakkinen's past activity with ACC or Gradient's past associations with VCCEP sponsors will impair Dr. Hakkinen's scientific objectivity as a VCCEP toluene panel member.

Dr. Elaine Cohen Hubal

Dr. Elaine Cohen Hubal is currently employed as a senior scientist in U.S. EPA's National Center for Computational Toxicology. The NCCT has a mission to integrate modern computing and information technology with molecular biology to improve Agency prioritization of data requirements and risk assessment of chemicals. The focus of Dr Hubal's research is on applying a systems approach to characterize complex relationships between environmental factors and health outcomes. Previously, she was Acting Associate Director for Human Exposure Modeling in the Human Exposure and Atmospheric Sciences Division of the U.S. EPA's National Exposure Research Laboratory (NERL) where she worked to develop and direct NERL's human exposure modeling research program. The NERL research program is designed to develop modeling tools and conduct modeling analyses to characterize and estimate human exposure to environmental pollutants and to reduce uncertainty in risk assessments for the general population and for highly-exposed subpopulations. A significant focus of the lab's human exposure research program is on understanding and characterizing children's residential exposures to environmental contaminants. She previously worked as a chemical engineer for the Research Triangle Institute, and Camp Dresser and McKee. She also served as a Predoctoral Fellow at the Chemical Industry Institute of Toxicology.

Dr. Hubal received her Ph.D. and M.S. in Chemical Engineering from North Carolina State University and a S.B. in Chemical Engineering from Massachusetts Institute of Technology. Dr. Hubal has served on a variety workgroups, panels, and committees. She currently serves as a member of EPA's Risk Assessment Forum and of the steering committee for ILSI Health and Environmental Sciences Institute's Biomonitoring Workgroup.

Dr. Hubal's current research interests focus on characterizing exposure-to-dose relationships and enhancing quantitative risk assessment through application of computational tools and a systems approach. Her general research interest is on reducing uncertainty in risk assessment with a specific focus on children's exposure. She has designed and conducted studies to evaluate dermal exposure assessment approaches and collect exposure factor data in support of the Food Quality Protection Act. She has developed and worked with a variety of computational models to describe the simultaneous mass transport and reaction of inhaled gases in the airway lining. Dr. Hubal has also worked on the development of a modeling platform to predict contaminant fate and transport of environmental pollutants to perform exposure assessments in support of the Hazardous Waste Identification Rule, and conducted research in the area of industrial pollution prevention by developing a framework to evaluate the environmental impact of pollution prevention activities that directly relates the energy requirements to process air, water, and solid waste emissions.

Dr. Hubal has published in the areas of children's exposure and human health risk modeling.

Dr. Hubal is a core panel member. She was selected for the core panel because of her expertise in evaluating exposure-to-dose relationships and her experience in using computational models with the mass transport of inhaled gases and other substances.

Disclosure

Dr. Hubal is employed by the U.S. EPA, which has taken public positions on the VCCEP pilot chemicals, including toluene. The comments that Dr. Hubal makes during this meeting are her personal opinions, and her opinions should not be construed to represent the opinions of the U.S. EPA.

TERA has determined that Dr Hubal has no conflicts of interest.

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.

Dr. Kacew is a core panel member. He was selected for the core panel because of his experience in toxicology and risk assessment, as well as his familiarity with the potential impact of environmental contaminants on children's health.

Disclosure

None

TERA has determined that Dr Kacew has no conflicts of interest.

Dr. Chad Sandusky

Dr. Chad Sandusky is currently Director of Research and senior toxicology advisor to the Physicians Committee for Responsible Medicine (PCRM), a non-profit organization that promotes good nutrition, conducts clinical trials and promotes non-animal experimental methods in medical and scientific research. For PCRM, Dr. Sandusky coordinates the review and preparation of comments on the EPA's High Production Volume Challenge Program (HPV) and Voluntary Children's Chemical Evaluation Program (VCCEP) chemical assessments. As such, he stresses the weight-of-evidence approach in these assessments and the development of exposure scenarios as key to the success of these programs. He is actively engaged in identifying methods which use alternatives to animal testing to meet the needs of the safety assessments, including tests undergoing validation at the European Center for Alternative Methods (ECVAM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).

Dr. Sandusky was the past Manager of Toxicology and Risk Assessment at ENVIRON and has extensive experience at both the EPA and ENVIRON in pesticide toxicology as well as exposure and risk assessments. For example, he evaluated the toxicology of pesticides and extrapolated these effects in risk assessments; directed the dietary exposure and risk assessments for agrochemicals and other potentially toxic residues in foods using the TAS Dietary exposure software; served as toxicology team leader and senior author of numerous EPA documents, including Registrations Standards and Position Documents; and since the passage of the FQPA in August 1996, coordinated the review and assessment of numerous agrochemicals to address the full range of new requirements, including: assessing aggregate exposure from multiple pathways (e.g., drinking water and residential use), cumulative exposure to chemicals with a common mode of action, accounting for potential sensitivity to infants and children, and assessing the potential for endocrine disruption.

Dr. Sandusky has extensive international experience including the coordination and submission of dossiers for the EU Reauthorization process under EU 91/414 and presentation of the results to member states. Dr. Sandusky also represented the Institute of Food Technology at the Codex Committee for Pesticide Residues (CCPR) in The Hague for several years. In addition, he also coordinated preparation and reviews of dossiers for chemicals approved as GRAS as well as directed the preparation and submission of Food Contact Notifications (FCNs) to the FDA. More recently, Dr. Sandusky represented the International Coalition of Animal Protection Organizations (ICAPO) at the OECD meetings in Paris on the Existing Chemicals Programme.

Dr. Sandusky received his Ph.D. in Pharmacology from the Emory University. He served as a Postdoctoral Fellow at the Georgetown University Schools of Medicine and Dentistry, Washington, D.C. He is currently a member of the Society of Toxicology, and he was previously affiliated with such organizations as the International Society of Exposure Analysis and the Society of Environmental Toxicology and Chemistry.

Dr. Sandusky is a core panel member. He was selected for the core panel because of his expertise in toxicology and pharmacology, in risk assessment, and his extensive knowledge of animal welfare issues.

Disclosure

Dr. Sandusky is currently is employed by the Physicians Committee for Responsible Medicine (PCRM), which has taken public positions on the VCCEP pilot chemicals, the tiered test methods, and on the

VCCEP program itself. Several years ago, Dr. Sandusky did consulting work for Shell and Chevron, related to their agricultural chemicals business.

TERA has determined that Dr. Sandusky has no conflicts of interest. His employment by PCRM and past consulting work are being disclosed to assure transparency. *TERA* does not believe these activities will impair Dr. Sandusky's scientific objectivity as a VCCEP toluene 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 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.

Dr. Vorhees is an *ad hoc* panel member. She was selected for the toluene panel because of her experience in the evaluations of general and site-specific exposures and her familiarity with probabilistic human exposure models. She has published on the importance of uncertainty and variability to predicted risks (*Risk Anal., 2002*).

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 toluene 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 toluene, and Dr. Vorhees herself was and is not involved in the MCA work.

TERA has determined that Dr Vorhees has no conflicts of interest. 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 toluene panel member.

Dr. Clifford Weisel

Dr. Clifford Weisel is a Professor in the Department of Environmental and Occupational Medicine at the Robert Wood Johnson Medical School-University of Medicine and Dentistry of New Jersey (RWJMSUMDNJ). He also holds an appointment in the UMDNJ School of Public Health and in the Graduate School of Rutgers University through the Department of Environmental Sciences. He is the director the Graduate Program in Exposure Sciences, a joint doctoral degree program through the Graduate School of Biomedical Sciences of UMDNJ and Rutgers University. He is the deputy director of the Exposure Sciences Division of the Environmental and Occupational Health Sciences Institute. His teaches courses on measurement techniques of exposure and environmental sciences to graduate students and the importance of exposure analysis to medical school students. His current research involves determining multi-route (inhalation, dermal and ingestion) exposures to environmental contaminants; the association between indoor, outdoor and personal air levels; understanding the association between exposure uptake and toxicokinetics; the association between health effects, such as asthma and cardiovascular disease, and exposure to air pollutants; and identification of populations susceptible to chemical exposure due to genetic differences.

Dr. Weisel received his Ph.D. in Chemical Oceanography from the University of Rhode Island. He was a National Research Council Postdoctoral Fellow at the National Oceanographic and Atmospheric Administration Laboratory in Miami, FL, and a research scientist with City University of New York before joining the faculty of UMDNJ in 1989.

Dr. Weisel has served on numerous expert panels and committees, including as a member of the National Advisory Science/Institute of Medicine Committee on Agent Orange. He has been on panels for the USEPA, NIEHS, American Chemistry Council, and the International Life Sciences Institute. He has been a session chair at numerous International Society of Exposure Analysis meetings and presented invited lectures at variety governmental agencies, colleges and universities, and at international workshops and meetings. He conducted the RIOPA (Relationships of Indoor, Outdoor, and Personal Air) study published recently by the Health Effects Institute and the Mickey Leland National Urban Air Toxics Research Center.

Dr. Weisel has been a grant reviewer for the US EPA, NIEHS, the American Chemistry Council and American Water Works Association and has served as an external referee for dozens of journals. He currently is the Associate Editor of the *Journal of Exposure Analysis and Environmental Epidemiology*, and has served as an Associate Editor for *The Journal of the Air Waste and Management Association.* He is a founding member of the International Society of Exposure Analysis, served as Treasurer of that society for three years and is currently its President elect. Dr. Weisel has over 60 publications in peer-reviewed journals and several book chapters in the area of exposure assessment, environmental health and public health.

Dr. Weisel is an *ad hoc* panel member. He was selected for the toluene panel because of his experience in assessing multi-route exposures to environmental contaminants, together with his knowledge of the association between exposures, toxicokinetics, and health effects in susceptible populations. Dr. Weisel's recent publications include reports on source proximity and outdoor-residential VOC concentrations from the RIOPA study (*Environ. Sci. Technol., 2006*) and findings of fine organic particulate matter in RIOPA homes (*J. Expo. Sci. Environ. Epidemiol., 2006*).

Disclosure

Dr. Weisel is a co-investigator on a university grant from the American Chemistry Council (ACC) for diagnostic evaluation and refinement of procedures modeling exposures to volatile organic hydrocarbons, including toluene. He conducted the RIOPA (Relationships of Indoor, Outdoor, and Personal Air) study published recently by the Health Effects Institute and the Mickey Leland National Urban Air Toxics Research Center.

TERA has determined that Dr. Weisel has no conflicts of interest. His co-investigator status on a university grant from ACC and work on RIOPA are being disclosed to assure transparency. *TERA* does not believe these activities will impair Dr. Weisel's scientific objectivity as a VCCEP toluene panel member.

Sponsor Presenter Biographical Sketches

Dr. John Bukowski

Senior Associate
WordsWorld Consulting

Dr. John Bukowski is a senior associate at WordsWorld Consulting, a biomedical and medical-writing consultancy located in Dayton, Ohio. He provides research assistance on epidemiology and public/occupational health, as well as general assistance on issues relating to clinical medicine. His epidemiology and public health career has spanned 20 years, including a broad base of experience within government, academia, and private industry. His clinical research experience includes a post as Director of the Clinical Research Centre at the University of Prince Edward Island, Canada. He has most recently worked as a senior scientist and epidemiologist for ExxonMobil Biomedical Sciences, focusing on such varied topics as children's health, reproductive health, neurological health, solvent exposure, risk assessment, and emerging health issues. During his career, he has authored numerous peer-reviewed articles as well as a multitude of reports, critiques, reviews, and white papers. John has a Masters in Public Health from the University of Michigan and a Ph.D. in epidemiology from the University of Medicine and Dentistry of New Jersey. He also has a doctorate in veterinary medicine from Michigan State University, and practiced clinical medicine for several years. He sits on the Editorial Board for the journal Nonlinearity in Biology, Toxicology, and Medicine and is an Adjunct Associate Professor at the University of Medicine and Dentistry of New Jersey.

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. 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

Sponsors' Presentation Slides

Toluene VCCEP Assessment

TERA Peer Consultation Meeting
November 7-8, 2006

Andrew Jaques,
American Chemistry Council

Outline for Presentations

Introductions/Background:
Andrew Jaques, ACC Consortium Manager

Hazard Assessment:
Dr. Ceinwen Schreiner, C&C Consulting
Dr. John Bukowski, Words World Consulting

Exposure Assessment:
Julie Panko, ChemRisk

Risk Assessment:
Sean Hays, Summit Toxicology

VCCEP Data Needs Assessment:
Andrew Jaques

Toluene Tier 1 VCCEP Sponsors

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

VCCEP Selection Basis

- Toluene 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.
- Low/moderate water solubility (0.5 g/L @ 25^{o}C).
- Biodegradable.
- Low bioaccumulation/bioconcentration.
- TRI emissions are mostly to air (96%); emissions have been reduced by approximately 2/3rd since 1990.

Chemical Background (2)

- Most toluene production is not in isolated form, but as a component of petroleum streams primarily used in gasoline (gasoline typically contains about 5% toluene).
- The majority of isolated commercial toluene production is used in the manufacture of the other aromatic hydrocarbons (benzene, xylenes).
- Approximately 20% used in solvent and other applications.
- A small portion of isolated commercial toluene is blended back into gasoline to improve octane ratings.
- By-product of combustion (mobile sources, biomass burning, cigarette smoke).

Regulatory Overview

- Toluene 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;
  - Consumer Product Safety Commission (CPSC) child-resistant packaging regulations.

Toluene VCCEP Hazard Assessment: Animal Toxicology

November 7, 2006

Dr. Ceinwen Schreiner
C&C, Consulting in Toxicology

Hazard Assessment: Introduction

Extensive toxicology data are available on toluene to address all 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 > 5g/kg	non-toxic
• Acute dermal [rabbit, guinea pig]:	
– LC50 > 12g/kg	non-toxic
• Acute inhalation [rat]: 4 hr exposure	
– LC50 > 28g/m^3 [7503ppm]	non-toxic
• Skin irritant	
• Moderate eye irritant	
• Not a skin sensitizer	

All Tier 1 Endpoints are met (cont.)

- **Genetic Toxicity *In Vitro***
  - Bacterial assays: Negative ±S9
  - Mammalian Cells: Negative - chromosomes, micronuclei, SCE
- Repeat Dose Screening studies are superceded by Tier 2 studies.

Tier 2 Endpoints

- **Genetic Toxicity *In Vivo***
  - Micronucleus assay: Negative
    Intraperitoneal: Mice (Mohtashamipur et al., 1985, 1987)
    NOAEL = 435mg/kg administered twice, 24 hr apart
  - Chromosome aberrations: Negative
    Oral: Mice (Gad-El-Karim et al., 1984)
    NOAEL = 1720mg/kg single dose: no increase in chromosome or micronuclei
  - DNA damage: Negative
    Inhalation: Rat (Plappert et al., 1994)
    8 week exposure; single cell starch gel electrophoresis
    NOAEL = 500ppm, No effect in peripheral blood, liver and bone marrow cells.
  - Dominant Lethal assay: Negative
    Inhalation: Mice, 6hr/d, 8 weeks NOAEL = 400ppm (API, 1981)
    no increase in pre- or post-implantation losses
  - **Toluene does not cause cytogenetic damage.**

Tier 2 Endpoints (cont.)

- **Repeat Dose Studies**
  - **Inhalation:**
    - **Rats and Mice, 14-15 weeks** [NTP, 1990]
      Doses: 0, 100, 625, 1250, 2500, 3000ppm
      Rats: LOAEL = 1250ppm; death, body and organ weight changes, ataxia, decreased leukocytes in females
      Mice: LOAEL = 100ppm; death, body and organ weight changes
      No adverse effects on sperm or estrus cycle in either species
    - **Rats, Male, 3-6 months** [Korsak et al., 1992]
      Doses: 0, 1000ppm for 3 months or 0, 100ppm for 6 months
      LOAEL = 1000ppm, 3 months; decreased circulating lymphocytes, increased monocytes, decrement in rotarod performance and reduced spontaneous activity
      NOAEL = 100ppm, 6 months

Tier 2 Endpoints (cont.)

- **Repeat Dose Studies: (cont.)**
  - **Oral:**
    - **13 week study, Rats and Mice** [NTP, 1990]

      Doses: 0, 312, 625, 1250, 2500, 5000mg/kg/day

      Rats: LOAEL = 625mg/kg/day; death, hypoactivity, ataxia, increased liver and kidney weights, neuropathological changes in brain

      NOAEL = 312mg/kg/day

      Kidney weight data used in calculation of RfD.

      Mice: LOAEL = 312mg/kg/day; death, hypoactivity, prostration, ataxia, organ weight changes

Tier 2 Endpoints (cont.)

- **Developmental Toxicity:**
  - **Inhalation, Rats**
    - Doses: 0, 600, 2000ppm, 6hr/day, Gest day 7 - 17 [Ono et al., 1995]
      NOAEL = 600ppm
      Caesarean section Gest 20: no significant effects on reproductive parameters.
      Delivered offspring: 2000ppm - decreased pup weight; non-significant effect on learning [small sample size]
    - Doses: 0, 250, 750, 1500, 3000ppm, 6hr/day, Gest day 6-15 [API, 1992]
      LOAEL = 1500ppm, decreased maternal and fetal weights, skeletal variations and delayed ossification
    - Similar effects reported in rabbits and mice
  - **Oral, Rats** [Gospe et al., 1994, 1996, 1998]
    - Doses: 0, 520mg/kg/day or 0, 650mg/kg/day, 6hr/day, Gest day 6 -19
    - Decreased maternal weight gain, fetal body and organ weight, delayed ossification
  - **No toluene-induced malformations in developmental toxicity studies**

Tier 2 Endpoints (cont.)

- **Transplacental Absorption:**
  - **Inhalation : Mice** [Ghantous and Danielsson, 1986]

    Doses: 0, 2000ppm ^{14}C toluene 10 min. on Gest day 11, 14, 17; measured at 0, 1, 4, and 24 hours post exposure.

    Results:
    - 60% toluene absorbed by maternal tissue, rapidly eliminated.
    - Uptake in placenta and fetus/embryo within 1 hour but lower than maternal uptake [approx. 4% of that in maternal brain]
    - Rapidly eliminated within 4 hours.

Tier 2 Endpoints (cont.)

- **Reproductive Toxicity**:
  - **Inhalation: 2-generation Rat** [Roberts et al., 2003]

    Doses 0, 100, 500, 2000ppm, 6hr/day;

    Male & Female (F0 &F1) - 80 days plus 15 days mating; F0 female - Gest day 0-20, Lact day 5-20, 7 days/wk; F1 females - Gest day 0-20.

    2000ppm only to males and females mated with untreated partners

    Results: No effects on fertility,gestation, pup viability, no malformations
    - No microscopic abnormalities in reproductive organs in F0, F1 or F2 generations
    - LOAEL = 2000ppm, decreased pup weight for maternally exposed groups [both sexes treated; females only treated]
    - NOAEL = 500ppm
    - NOAEL = 2000ppm male only treated group

Tier 2 Endpoints (cont.)

- **Reproduction and Male Fertility**
  - **Inhalation:** [Ono et al., 1996]

    Doses: 0, 600, 2000ppm, 6hr/d Rats: Males 90 days including mating; Females 14 days + mating to Gest day 7, sacrificed Gest day 20

    Results: 2000ppm fetal mortality; increased dams with dead fetuses
    - Male fertility unaffected, decreased sperm count at both doses
    - No microscopic abnormalities in testes, epididymides or number of spermatogenic cells
  - **Inhalation: Males only** [Ono et al., 1999]

    Doses: 0, 4000, 6000ppm, 2hr/day, 5 weeks

    Results: LOAEL = 6000ppm, reduced epididymal sperm count, motility, and quality. No effect on testes weight or spermatogenesis

    NOAEL = 4000ppm
  - **Inhalation: Pups exposed *in utero*** [Dalgaard et al., 2001]

    Doses: 0, 1200ppm, 6hr/day, Gest day 7-18

    Results: No effect on sperm quality or computer assisted sperm analysis

Tier 2 Endpoints (cont.)

- **Immunotoxicity**
  - **Oral gavage, Female Mice** [Burns et al., 1994]

    Doses: 0, 600mg/kg/day, 14 days
    - No effects on thymus weight, PFC response, NK cells activity, delayed hypersensitivity response or host-resistance
    - Lower tumor incidence in fibrosarcoma challenged mice.
  - **Drinking water, Male mice** [Hsieh et al., 1989, 1990]

    Doses: 0, 17, 80 or 405mg/L (0, 5, 22, or105 mg/kg/d), 28 days

    LOAEL = 105mg/kg/d, Increased relative liver weight, decreased thymus weight, depressed lymphocyte proliferation, IL-2, antibody (PFC) response

    Doses: 0, 80, or 325mg/L (0, 22 or 85mg/kg/day), 28 days
    - No organ weight changes; Slight PFC reduction at 85mg/kg;
    - Inhibition of culture response to YAC-1 cells at both doses of uncertain significance
  - **Overall, results indicate that toluene is not significantly immunotoxic.**

Tier 2 Endpoints (cont.)

- **Toxicokinetics and Metabolism**
  - Absorption rapid by inhalation and ingestion; slow dermal absorption with significant evaporation in animals and humans.
  - Distribution is rapid throughout body, partitions into fatty tissue.
  - Primary metabolism occurs in liver via CYP 2E1
  - Major initial metabolite in animals and humans is benzyl alcohol; 75-80% absorbed toluene metabolized to benzoic acid. Cresol is a minor metabolite.
  - Conjugates of oxygenated metabolites are rapidly excreted in urine; 65-70% as glycine conjugate [hippuric acid], 0.1-0.4% as glucuronide and sulfate derivatives of cresol.
  - Elimination of unmetabolized toluene occurs by exhalation.

Tier 3 Endpoints

- **Chronic Toxicity/Carcinogenesis: Rats and Mice**
  - **Inhalation, 104 weeks**: [NTP, 1990, Huff et al., 2003]

    Rats: 0, 600, 1200ppm, 6hr/day, 5 days/week
    Mice: 0, 120, 600, 1200ppm, 6hr/day, 5 days/week
    - **Systemic toxicity:**

      Rats: nephropathy at 2000ppm; degeneration of olfactory and respiratory epithelia at both doses

      Mice: females lower body weight at 1200ppm
    - **Carcinogenicity:**

      Rats: No increases in any tumor type

      Mice: No significant tumor induction [females- increase in benign pituitary adenomas at 600ppm only]

Tier 3 Endpoints (cont.)

- **Adult Neurotoxicity**
  - **Inhalation, Rat** [Ladefoged, et al., 1991]
    Doses: 0, 500, 1500ppm, 5 days/week, 6 months, 2 month recovery
    NOAEL neurobehavioral effects = 1500ppm
    LOAEL brain physiology = 500ppm, reduction in hippocampus weight, alteration of norepinephrine, dopamine , 5-hydroxytryptamine
  - **Inhalation, Rat** [Von Euler et al., 2000]
    Doses: 0, 80ppm, 6 hr/day, 5 days/week, 4 weeks
    Slight deficit in spacial learning and memory, increase in dopamine receptors, decreased cerebral cortex size.
  - **Inhalation, Rat Auditory toxicity** [Pryor et al., 1984]
    Ototoxicity induced by combination of concentration x duration of exposure
    LOAEL = 1000ppm, 14hr/day, 7days/week for 2 weeks
    NOAEL = 700ppm, 14hr/day, 7 days/week for 2-16 weeks

Tier 3 Endpoints (cont.)

- **Developmental Neurotoxicity**
  - **Inhalation, Rat** [Hass et al., 1999]
    OECD 426: 0, 1200ppm, 6 hrs/day, Gest day 7- Postnatal day 18
    Lower pup weight until postnatal day 10, delayed ontogeny of some reflexes.
    Behavioral effects: increased motor activity at weaning; changes in water maze performance at 3 months
  - **Drinking water, Mice** [Kostas and Hotchin, 1981]
    0, 16, 80, 400ppm (0, 7.2, 14.4, 72mg/kg/day), Gestation to Lact. day 21
    NOAEL developmental = 72mg/kg/day
    LOAEL neurobehavioral = 72mg/kg/day, open field behavior habituation decreased at 35 days postnatal; rotarod performance impaired with inverse dose response at 45-55 days postnatal.
  - **Developing organism does not appear to be more sensitive than adult.**

Hazard Conclusions

- Extensive toxicity data are available to address VCCEP hazard endpoints
- Acutely non-toxic by oral, dermal or inhalation routes according to hazard classification
- Irritating to eye and skin
- Non-genotoxic
- Non-carcinogenic
- Unlikely to be immunotoxic

Hazard Conclusions (cont.)

- Reproductive performance and fertility unaffected by exposure to toluene
- Developmental toxicity expressed as low offspring weight and ossification delays occurs primarily at maternally toxic levels.
- Developmental and postnatal neurotoxicity have been reported.
- Neurotoxicity at moderate/high doses expressed as neuromuscular effects and impairment of sensory functions. Most sensitive endpoint for hazard and risk assessment.

Toluene VCCEP Hazard Assessment: Epidemiology Review

TERA Peer Consultation Meeting
November 7-8, 2006

John A. Bukowski, DVM, MPH, PhD
WordsWorld Consulting

Overview

- Reproductive associations
  - Spontaneous abortion
  - Infertility
- Neurological associations
  - Symptoms
  - Neurobehavioral tests
  - Sensory associations
- Uncertainty/Bias/Conclusions

Note: values reported are 8-hr TWA chronic occupational exposures

Reproductive Associations

- Occupational evidence for spontaneous abortion
  - Strongest association in Ng et al. (1992a) – 88 ppm
    - Limitations tend to inflate relative risk
- Limited data on infertility
  - Association from maternal (not paternal) exposure in Plenge-Bönig and Karmaus (1999)
    - Substantial limitations include subjective outcomes, probable confounding, and high potential for selection bias (39% participation among exposed women)
- Case reports "suggest" a syndrome similar to fetal alcohol syndrome from toluene abuse during pregnancy

Neurobehavioral Associations

- Symptom surveys
  - Inconsistent evidence (positive and negative)
  - Common, subjective, and transient complaints
    - Generally the same types of symptoms seen in clinical experiments
    - Substantial uncertainty associated with symptom data
  - Symptoms may be related to peak exposures
    - Up to 3000 ppm

Neurobehavioral/Psychometric Studies

- Exposures above 50 ppm may produce measurable neurobehavioral effects (especially short-term memory)
  - LOAEL approximately 90-100 ppm.
  - Several high-exposure studies reported totally/largely negative findings
- Studies with average exposure < 50 ppm were largely negative
  - NOAELs in the range of 20-30 ppm for recent exposure and 45-100+ ppm for long-term (past) exposure.
  - LOAELs and NOAELs overlap considerably
- Limitations
  - Volunteer samples
  - Largely cross-sectional snapshots
  - Exposure heterogeneity/misclassification

Neurobehavioral Epidemiology Investigations

	<50 ppm				>50 ppm			
Study	**M**	**A/C**	**P**	**PM**	**M**	**A/C**	**P**	**PM**
Cherry et al (1984)					-	-	-	+
Chia et al (1987)					-	-	NA	+
Hanninen et al (1987)					-	NA	-	-
Orbaek & Nise (1989)	-	-	-	-				
Foo et al (1990)					+	-	+	+/-
Boey et al (1997)					+	+	+	+
Eller et al (1999)	-	-	-	-	+	-	+	-
Gericke et al (2001)	+	-	-	NA				
Deschamps et al (2001)					-	-	-	-
Seeber et al (2002) & Zupanic et al (2002)	-	-	-	-				
Chouaniere et al (2002)	+	-	-	NA				

M= memory

A/C= attention / concentration

P= perception

PM= psychomotor

Neurobehavioral Conclusions

- Subjective complaints more common at higher exposure levels (eg, 50-100+ ppm)
- May be subtle neurobehavioral differences at >50 ppm
  - Most consistent association with short-term memory
- Minimal associations for occupational exposures <50 ppm
- Overall findings indicate that impact is mild and generally reversible
  - Subtle, rather than overt clinical effects
    - No noticeable impairment, inability to perform jobs, loss of quality of life
    - Neurological exams normal -- no signs of neuropathology or psychopathology
  - Effects generally appeared to be reversible
    - Little significant association after 48-hr withdrawl
    - Not correlated with duration of exposure.

Sensory Associations

- Evoked potentials
  - Visual or auditory
- Color discrimination
- Hearing

Visual / Auditory Evoked Potentials

- Test sensory nerve pathways
- Subtle associations as low as 40-60 ppm (Vrca studies)
  - Peak exposures much higher
- Limitations
  - Only two small worker populations
  - Potential for biased control selection and for confounding

Color discrimination

- Most sensitive indicator of chemical exposure
  - Lanthony D-15 and Color Confusion Index most common metrics
  - Basis for Rfc (5 mg/m^3 ≈ 1 ppm)
- No effect from high-level acute exposure
  - Up to 300-400 ppm
- Chronic exposure >100 ppm associated with decreased discrimination
  - Results near 50 ppm inconsistent
    - LOAELs 32-42 ppm, but NOAELs 30-56 ppm
  - Limitations
    - Potential for selection bias (volunteerism)
      - basic differences on sociodemographics
    - Mixed-solvent coexposures
    - Some incongruous or inconsistent results

Hearing

- X-sectional results suggest toluene exposures >> 50 ppm may be associated with mild hearing loss
  - Limitations include potential for selection bias, confounding from noise and mixed solvents, uncertain exposure metrics, and inconsistent results
- Findings from 5-yr. longitudinal analysis (Schaper et al. (2003)) suggest levels near 50 ppm are not associated with significant loss

Sensory Conclusions

- High-level toluene exposures (often > 100 ppm) are associated with sensory effects
- Data for exposures ≤ 50 ppm are equivocal
- Hearing loss is not a sensitive marker of exposure
- Most sensitive marker appears to be color discrimination
  - LOAELs as low as 32-42 ppm
  - LOAELs overlap with NOAELs from other studies.
- Overall findings indicate that sensory impacts from toluene are subclincial, without apparent effects on quality of life
  - No apparent permanent changes, CNS disorders, visual acuity problems, loss of job skills, or decreased quality of life.
    - Research suggests that color vision impairment is reversible after approximately one month without solvent exposure
      - Based on Triebig et al. (2001) on styrene

Uncertainty and Bias

- Potential for publication bias
  - PB in-situ most problematic (Phillips, 2004)
    - Form of selective analysis and reporting
    - Evidence from the literature (Boey et al., 1997)
- Multiple comparisons
  - Especially when there are multiple outcome-exposure combinations (eg, symptom surveys and neurobehavioral test batteries)
- Exposure heterogeneity
  - Tends to underestimate NOAELs and LOAELs

Overall Epidemiology Conclusions

- Some evidence of spontaneous abortion associated with occupational exposure > 50 ppm
  - Limitations preclude strong/causal conclusion
- Symptoms and subtle neurobehavioral changes probable for exposures > 50 ppm
  - Headache, irritation, short-term memory loss
    - Symptoms are especially difficult to interpret
  - Appear to be temporary
- Sensory changes are most sensitive effects
  - Exposures ≥ 100 ppm associated with evoked potential, color vision, and hearing changes
  - LOAEL of 32-42 ppm, but overlap with NOAEL
  - Subtle effects that appear to be temporary
- Overall findings support RfC as a health-protective value

Toluene VCCEP Exposure Assessment

TERA Peer Consultation Meeting
November 7-8, 2006

Julie Panko,
ChemRisk

Overview

- Focused on pathways and routes of exposure relevant to children and prospective mothers.
- Grouped exposures by:
  - Background chronic ambient exposure
  - Source-specific chronic exposures
  - Source-specific short-term episodic/occupational 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 on
  - activity patterns
  - Recommendations of previous VCCEP peer-review panels
  - EPA Children's Exposure Assessment Guidance
- Prospective mothers were included for evaluation of human milk pathway relevant for infants.

Category	Age Group
Children	0-6 weeks old
	7-12 weeks old
	13 weeks – 12 months old
	1-5 years old
	6-13 years old
	14-18 years old
Prospective Mother	19-35 years old

Exposure Data Acquisition

- Review of toluene in commerce
  - Production data
  - Usage data
- Extensive search of:
  - Governmental databases containing measured toluene concentrations in air, food, and water.
  - Published literature:
    - Occupational exposure
    - Indoor air evaluations
      - –Residential
      - –School
    - General population personal exposure measurements
    - Human milk concentrations
- Consortium member companies for occupational exposure data

Background Exposures

- Ambient Air
  - Outdoor air
    - Rural and urban
  - Indoor air
    - In-home and in-school
- Dietary
  - Food
  - Water
  - Human milk

Source-Specific Exposures

Based on comprehensive evaluation of toluene use in commerce and the published literature:

- Gasoline
- Consumer Products
- Tobacco smoke
- Occupational

Background: Ambient Air – Outdoor

- Reviewed published literature and government databases as sources of exposure data.
- Used EPA's AirData database. The average concentration for 'all rural' and 'all urban' was used to characterize 'typical'. The 95th percentile was used to characterize 'high-end'.
- Ambient outdoor air concentrations have been steadily declining over time.
- EPA SCREEN3 model was used to evaluate exposures at fenceline of emitting facilities. Model results showed that fenceline exposures were equivalent to the high-end urban values.

Ambient Air Toluene Concentrations (µg/m³)		
Setting	**Typical**	**High-End**
Rural	1.4	2.9
Urban	3.6	9.2

Background: Ambient Air - Indoor

- Reviewed published literature
  - Outdoor influences and indoor sources contribute to overall indoor concentrations
  - Indoor > outdoor
  - Published literature not completely representative of all U.S.
  - Calculated indoor to outdoor delta to derive representative indoor concentrations
  - Calculated values are generally higher than the average or 95th percentiles reported in the literature.

Residential Indoor Air Toluene Concentrations (µg/m³)		
Setting	**Typical**	**High-End**
Rural	21	77
Urban	24	83

Background: In-School Air

•EPA conducted indoor air studies of schools from 1995-1998.
•Additional study completed for portable school buildings with similar results (Speilman, 2004).
•Published studies may not be representative of in-school air quality nationwide, as they are focused on "problem" buildings.

Exposure	In-School Toluene Concentration ($\mu g/m^3$)
Typical	3.9
High-end	65

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 toluene from food intake.

Ingestion of Toluene from Foods (mg/kg/day)		
Age Group	**Typical**	**High-End**
13 weeks to 1 year	0.000144	0.000319
1-5 years	0.000426	0.000716
6-13 years	0.000249	0.000448
14-18 years	0.000142	0.000320
19-35 years female	0.000118	0.000237

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 toluene from water.

Ingestion of Toluene from Tap Water (mg/kg/day)		
Age Group	**Typical**	**High-End**
0-6 weeks	0.0000584	0.000116
7-12 weeks	0.0000389	0.0000775
13 weeks to 1 year	0.0000250	0.0000498
1-5 years	0.0000261	0.0000556
6-13 years	0.0000116	0.0000237
14-18 years	0.00000698	0.0000148
19-35 years, female	0.00000824	0.00000162

Background: Human Milk

- Evaluated as a potential source of exposure for infants <1yr old.
- One published study (Fabietti et al, 2004) provided measured data from small sample of Italian women.
- Used pharmacokinetic model by Fisher et al (1997) to calculate toluene concentrations in human milk.
- Evaluated occupationally and non-occupationally exposed mothers.
- Non-occupational exposures similar to that observed by Fabietti et al. Modeled occupational values higher than Fabietti et al.

Scenario	Ingestion of Toluene from Human Milk (mg/kg/day)
Urban, typical	0.000035
Urban, high-end	0.00012
Occupational, typical	0.015
Occupational, high-end	0.055

Source Specific: Gasoline

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

Scenario	Typical Toluene Concentrations ($\mu g/m^3$)	High-End Toluene Concentrations ($\mu g/m^3$)
In-Vehicle	9.8	9.8
Refueling	1,400	4,700

Source Specific:
Consumer Products

- **Reviewed consumer product surveys**
  - Sack et al., 1992
  - EPA's Source Ranking Database (SRD)
  - National Library of Medicine Household Product Database
- **Consumer products that contained total toluene >1% by weight included 8 categories:**
  - Spray primer/paint/stain
  - Metal parts degreasing (paint thinner/ neat toluene)
  - Surface preparation (paint remover)
  - Spray shoe polish
  - Mixed media art (adhesives)
  - Wood restoration/cleaning
  - Automotive products
    - Battery cleaner/protector, carburetor and choke cleaner, belt lubricant/dressing
  - Nail polish

Source Specific:
Consumer Products (cont.)

- **Product categories likely to result in the highest exposures and be used in the presence of or by children:**
  - Metal parts degreasing
  - Paint-related products
  - Shoe polish
  - Mixed media art products
- **Reviewed the published literature and did not identify studies that contained toluene exposure measurements.**

Source Specific:
Consumer Products (cont.)

- **Developed exposure scenarios and used mathematical exposure models to estimate toluene exposure**
  - EPA Multi-Chamber Concentration and Exposure Model Version 1.2 (MCCEM)
  - EPA's Exposure, Fate Assessment Screening Tool Version 1.1 (EFAST)
- **Scenarios included:**
  - Residential metal parts degreasing
  - Residential spray painting
  - Residential spray shoe polish
  - Residential mixed media art

General Consumer Product Modeling Assumptions

- **Conservative (exposure enhancing) assumptions**
  - Product used indoors; although high end usage amounts likely to be used outdoors
  - Room of use was a small utility room (20 m^3 or 10'x10'x7', 700 ft^3)
  - For paint products and mixed media art scenario, evaluated consecutive uses of toluene containing products, which contained high end concentrations of toluene
  - Usage data from Westat, 1987.
- **Air concentrations modeled for room of use and rest of house (e.g. 2-zone model)**
- **Where indicated on product label directions, followed manufacturers instructions to use in well ventilated area**
  - Typical = one window open for whole house air exchange rate of 1.3 air changes per hour
  - High End = window open and fan operational for whole house air exchange rate of 5 air changes per hour

Source Specific:

Residential Metal Parts Degreasing

- Scenario for evaluating the use of solvent type cleaning fluid or degreaser.
- Commonly used as metal parts degreasers in hobbies such as firearm restoration or classic automobile restoration.
- Typical toluene content of solvent was 21%, high-end assumed to be 100%.
- Application of solvent was via wiping on with a cloth. Used EFAST 'product applied to surface' as baseline scenario.

Degreaser Usage Amount			
Usage	**Ounces/ Use[a]**	**Cups /use**	**Grams paint thinner/ use[a]**
Typical	0.4	0.05	9.8
High- end	4.0	0.50	98

Source Specific:

Residential Metal Parts Degreasing Model Results

Scenario	1-hr TWA Exposure (ppm)		8-hr TWA Exposure (ppm)		24-hr TWA Exposure (ppm)	
	Room of Use	Other Room	Room of Use	Other Room	Room of Use	Other Room
Typical	2.8	0.67	0.40	0.12	0.13	0.041
High-End	37	11	5.1	1.6	1.7	0.52

Source Specific:

Residential Spray Painting

- **Scenario consisted of two steps, spray primer application followed by spray paint application.**
- **Used EFAST 'product sprayed on surface' as the baseline scenario.**
- **Assumed that products would be used consecutively and based usage amounts on the Westat 1987 survey**
- **For high end, conservatively assumed that product user would use a primer and paint that both contained high-end toluene concentrations.**

Spray Paint Scenario Usage Amount

Product	Usage	%-ile	ounces/ use	ml/ use	can/ use	grams product/ use
Spray Primer	Typical	50th	8	237	0.54	185
	High end	90th	26	769	1.7	600
Spray Paint	Typical	50th	8	237	0.51	175
	High end	90th	26	769	1.7	569

Source Specific:

Residential Spray Painting Model Results

Scenario	1-hr TWA Exposure (ppm)		8-hr TWA Exposure (ppm)		24-hr TWA Exposure (ppm)	
	Room of Use	Other Room	Room of Use	Other Room	Room of Use	Other Room
Typical	37	11	10	3.0	3.2	1.0
High-End	70	20	15	4.7	5.0	1.6

Source Specific:

Residential Spray Shoe Polish

- **Used the Westat (1987) survey to obtain various scenario parameters.**
- **Depending on size of the shoe, typical use scenario was shining of 1-2 pairs of shoes (1/10th can) , high-end use represents 3 or more pairs of shoes (1/2 can).**
- **Used EFAST 'product sprayed on surface' as the baseline scenario.**
- **Assumed no open windows for typical scenario, but for high end scenario, we assumed an open window in accordance with label directions**

Spray Polish Usage Amounts (Westat, 1987)				
Usage	**ounces/ use**	**ml/use**	**cans/use**	**grams spray polish/use**
Typical (50th percentile)	1.02	30	0.1	30
High end (90th percentile)	5.74	170	0.5	167

Source Specific:

Residential Spray Shoe Polish Model Results

Scenario	1-hr TWA Exposure (ppm)		8-hr TWA Exposure (ppm)		24-hr TWA Exposure (ppm)	
	Room of Use	Other Room	Room of Use	Other Room	Room of Use	Other Room
Typical ACH=0.45	2.5	0.39	0.41	0.13	0.14	0.046
High-End ACH=1.34	45	11	6.4	2.0	2.1	0.66

Source Specific:

Residential Mixed Media Art

- **Scenario consists of use of non-aerosol adhesive and glass frosting spray to coat glass surfaces. (These are not children's arts and crafts products)**
- **Conservatively assumed that products would be used consecutively.**
- **Used EFAST 'product applied to surface' for adhesive and 'product sprayed on surface' for glass frosting spray as the baseline scenario.**

Mixed Media Art Scenario Usage Amounts

Product	Usage	ounces/ use	ml/ use	cans/ use	grams product/use
Adhesive	Typical (50th percentile)	0.25	7.4	--	6
	High end (90th percentile)	2	59	--	52
Glass frosting	Typical (50th percentile)	9	266	0.75	222
	High end (90th percentile)	26	769	2.2	641

Source Specific:

Residential Mixed Media Arts Cumulative Model Results

Scenario	1-hr TWA Exposure (ppm)		8-hr TWA Exposure (ppm)		24-hr TWA Exposure (ppm)	
	Room of Use	Other Room	Room of Use	Other Room	Room of Use	Other Room
Typical ACH=1.34	7.0	1.8	1.2	0.36	0.39	0.12
High-End ACH=5	98	29	20	5.9	6.7	2.0

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Source Specific:

Tobacco Smoke

- Evaluated environmental tobacco smoke (ETS) and mainstream smoke
- Published literature used to determine toluene emission rate
- Modeled toluene indoor air concentration due to ETS using MCCEM
- Estimated toluene intake from mainstream smoke

Toluene Exposures from Tobacco Smoke		
	Indoor Toluene Concentration from ETS ($\mu g/m^3$)	**Toluene Dose from inhalation of mainstream smoke (mg/kg-d)**
Typical	1.1	0.006
High End	1.5	0.01

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Source Specific:
Occupational

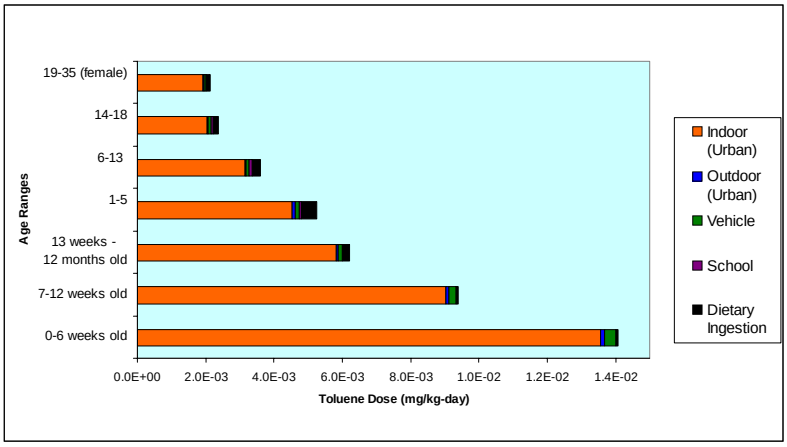
- Evaluated the published literature (>100 studies) and consortium member industrial hygiene data.
- Exposure concentrations were obtained from Caldwell et al (2002), which compiled exposures to U.S workers in solvent end-use occupations.
- Dermal exposures calculated using EASE. The dose was insignificant compared to the exposure via inhalation.

Scenario	Toluene Exposure Concentration 8-hr TWA ppm (mg/m^3)
Typical	6.5 (24)
High-End	23 (87)

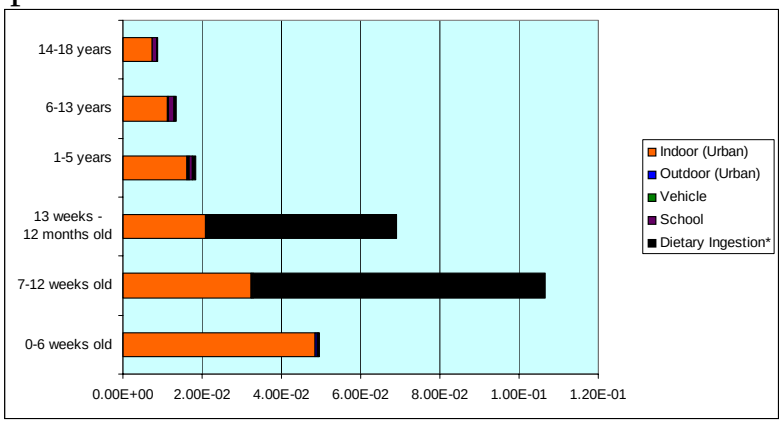
Aggregate Exposures

- **All exposure estimates converted to common unit of average daily dose (ADD) and expressed in terms of mg/kg-day.**
- **Age-specific exposure factors were used to calculate ADDs:**
  - **Body weight**
  - **Inhalation rate**
  - **Ingestion rate**
  - **Skin surface area**
  - **Time activity patterns**
- **For all age groups, except the nursing infant, inhalation was the primary exposure route.**
- **For nursing infants of occupationally exposed mothers, ingestion of human milk was the primary exposure route, followed by inhalation.**

Contribution of Various Sources to Typical Total Background Exposure

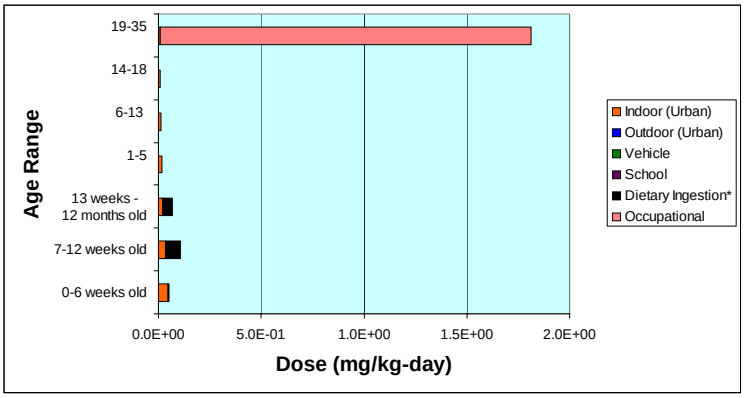


Contribution of Various Sources to High-end Chronic Exposures



*The doses for the 7-12 week old and 13 week-12 month old groups includes exposure from human milk of a high-end occupationally exposed mother.

Contribution of Various Sources to High-end Chronic Exposures



*The doses for the 7-12 week old and 13 week-12 month old groups includes exposure from human milk of a high-end occupationally exposed mother.

Conclusions

- Robust exposure data are available to evaluate background chronic exposure to toluene.
- Aggregate exposure analysis indicates inhalation of indoor air is the primary route/source of children's exposure to toluene.
- No child-specific exposure scenarios were identified, except ingestion of human milk from occupationally exposed mothers.

Toluene VCCEP Risk Assessment

TERA Peer Consultation Meeting
November 7-8, 2006

Sean Hays
Lesa Aylward
Summit Toxicology, LLP

Overview

- Toxicological criteria for assessment of exposures
- Implications of data on child-specific physiological and metabolic capability
- Risk assessment results

Hazard Assessment Findings Relevant for Risk Assessment

- Neurotoxicity is the most sensitive endpoint in humans
  - Underlying RfC derivation
- Kidney toxicity underlying RfD of less relevance
  - Large NOAEL from rodent study with large uncertainty factor (3000 vs. 10 used in RfC derivation)
  - Renal toxicity observed in humans only after high dose poisoning or chronic abuse
  - Kidney toxicity evaluated but not identified as a sensitive endpoint in studies of occupational populations
- Toluene pharmacokinetics well understood

Current EPA Hazard Assessment

	Study Description	Critical Endpoint	Uncertainty Factors	Value
RfC	Multiple studies, occupationally exposed populations	Neurological effects NOAEL=34 ppm Adj. 24/7=13 ppm	10	5 mg/m^3 (1.3 ppm)
RfD	Rat gavage, 13 wk (NTP, 1990)	Kidney weight changes BMDL (228 mg/kg/day), equal to experimental NOAEL	3000	0.08 mg/kg-d

Two Approaches for Assessing Potential Health Risks

- Administered toluene dose
  - Calculate hazard quotients by comparing:
    - Estimated oral doses or inhalation concentrations to RfD or RfC, respectively
    - Sum hazard quotients from different routes of exposure to obtain a hazard index (HI)
    - HI < 1 indicates no health risk
- Internal toluene dose (blood concentration)
  - Calculate HI by comparing modeled blood levels from identified exposures (all routes of exposure) to benchmark blood level
  - HI < 1 indicates no health risk

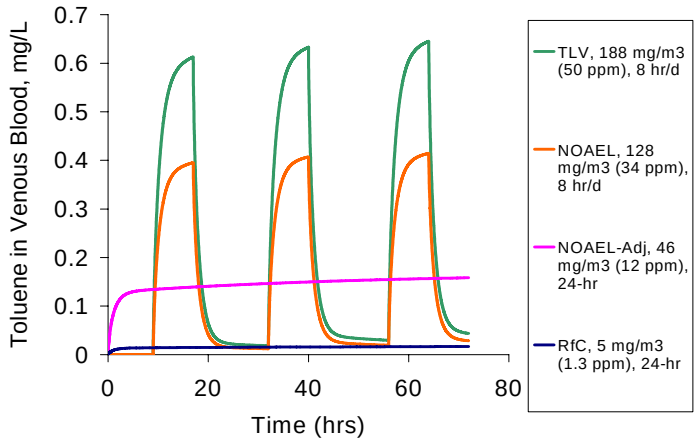
Why Use a PBPK-Based Approach?

- Pharmacokinetics of toluene straight-forward and well-understood
  - Human and rodent PBPK models based on controlled experimental data allow prediction of blood levels resulting from various exposure regimens
- Evaluate impact of temporal patterns of exposure
- Integrate exposures from multiple routes (oral and inhalation)
- Capture age-dependent changes in ADME and resulting potential sensitivities resulting from different blood toluene profiles

Identification of Blood Level Benchmark for Risk Assessment

- Using an internal dose metric requires choosing
  - Most appropriate endpoint
  - Internal dose metric associated with toxic response
- Neurotoxicity is the most sensitive endpoint identified in humans
  - Basis for the RfC
- Toluene blood levels have been found to be well-correlated with changes in neurological responses Benignus et al. (1998)
  - Consistent with observations on other solvents

Blood Levels Associated with the RfC and Underlying Exposure Levels



PBPK Model Results – Blood Levels Associated with the RfC and Underlying Data

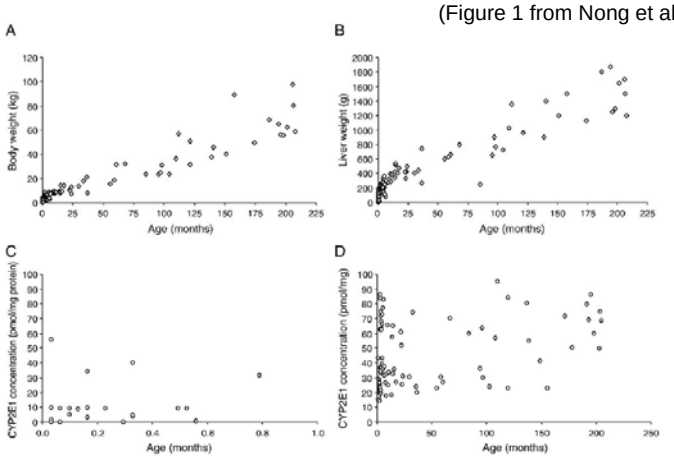
- Steady-state blood level associated with continuous exposure in adults:
  - RfC_{Blood} ~ 0.0175 mg/L
  - >30-fold lower than peak blood levels at the TLV
  - >20-fold lower than peak blood levels at the EPA-identified NOAEL of 34 ppm in occupationally-exposed individuals
  - 10-fold lower than the *average* blood levels at the NOAEL

Age-Specific PBPK Models for Toluene

- Developed by Nong et al. (2006)
- Incorporate detailed data on
  - Development of metabolic capability (CYP 2EI) in neonates, infants, and children
  - Age-specific physiological parameters (body weight, organ sizes and blood flows, lung ventilation rates, and cardiac output)
- Metabolic capability of children represented as a function of
  - Concentration of hepatic CYP2E1 protein, and
  - Liver volume

CYP2E1 Protein Concentration and Liver Volume Increase with Age in Children

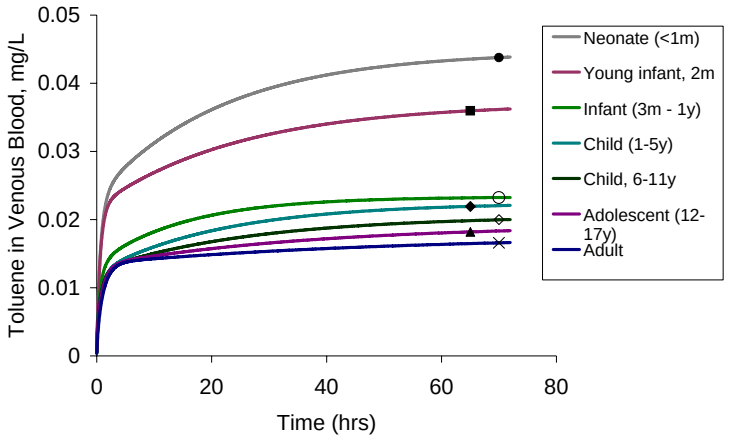
(Figure 1 from Nong et al. 2006)



Age-Specific PBPK Models for Toluene *(continued)*

- Children's models NOT experimentally validated
  - No controlled data examining blood levels as a function of external exposure levels in children
- However, the models provide a rational basis for examining the ***relative*** impact of known physiological and metabolic differences between children and adults
  - Lower metabolic capability leads to higher toluene blood levels in children than in adults for same exposure level
    - 2 to 3 times higher for neonates and young infants;
    - <2 times higher for older infants and children

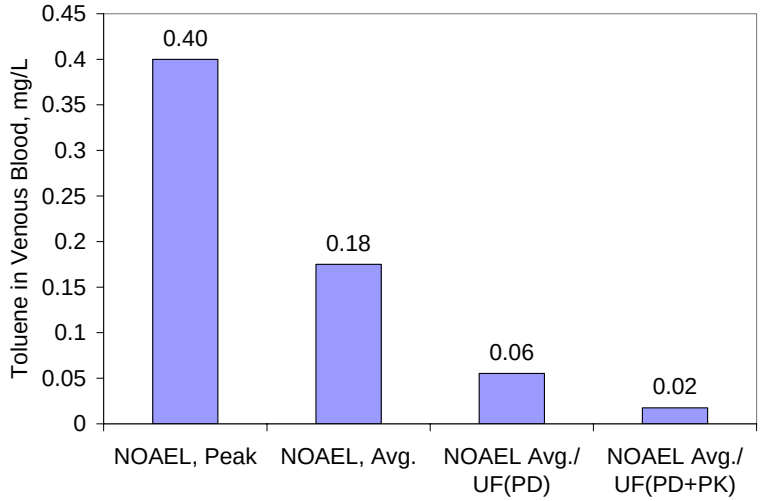
Modeled Blood Levels Inhalation at RfC, 5 mg/m^3 (1.3 ppm)



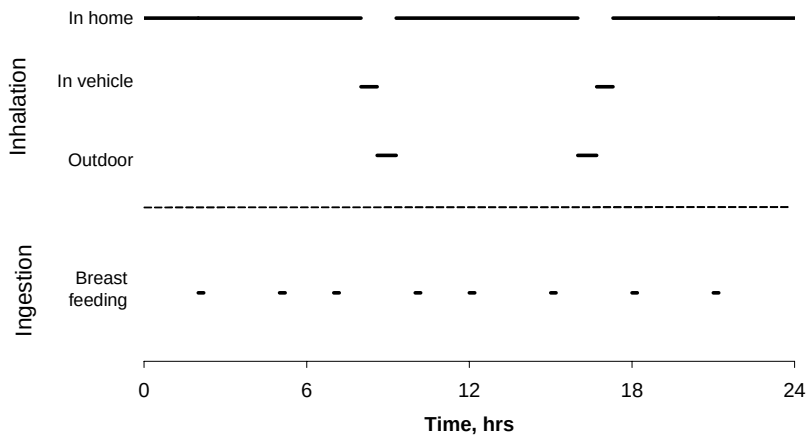
Intraindividual UF of 10

- Default UF of 10 typically considered to represent
  - ~3x for pharmacodynamic (PD) differences
  - ~3x for pharmacokinetic (PK) differences
- Replace default UF with modeling when information is available
- PD: No quantitative PD model available
- PK: Data available on age dependence of metabolic capability
  - Blood concentrations modeled for different age groups, e.g., PK variability is explicitly captured in internal dose assessment

Impact of UF on Toluene Blood Level Benchmark

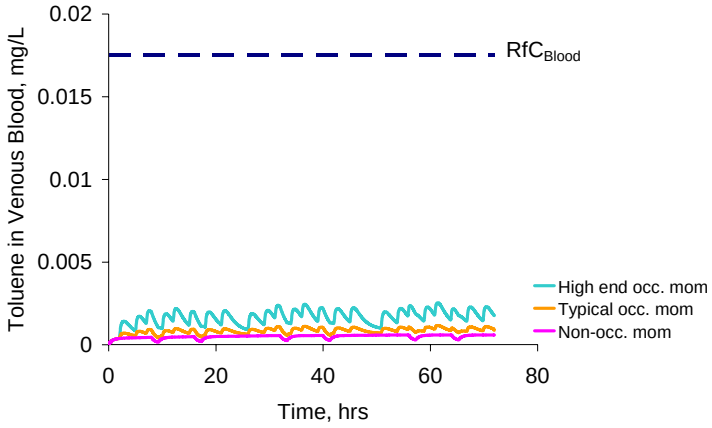


Time Pattern of Modeled Exposures, Infant, 7-12 wks



Predicted Blood Levels in Infants

Aged 2 m, High End Urban Air, Milk from Occupationally Exposed Mothers



Risk Assessment Results – Internal Dose

- Typical and high end hazard indices generally below 0.02
- Two scenarios with human milk from high-end occupationally exposed mother result in hazard indices ~ 0.1

Administered Dose Hazard Index (HI) Calculation

- HQ_{inhal}: Inhalation exposures (24-hour TWA in mg/m^3) compared to RfC (5 mg/m^3)
- HQ_{ingest}: Ingestion exposures (long-term average daily intakes in mg/kg-d) compared to RfD (0.08 mg/kg-d)
- $HI = HQ_{inhal} + HQ_{ingest}$

HI Calculation Example: Administered Dose

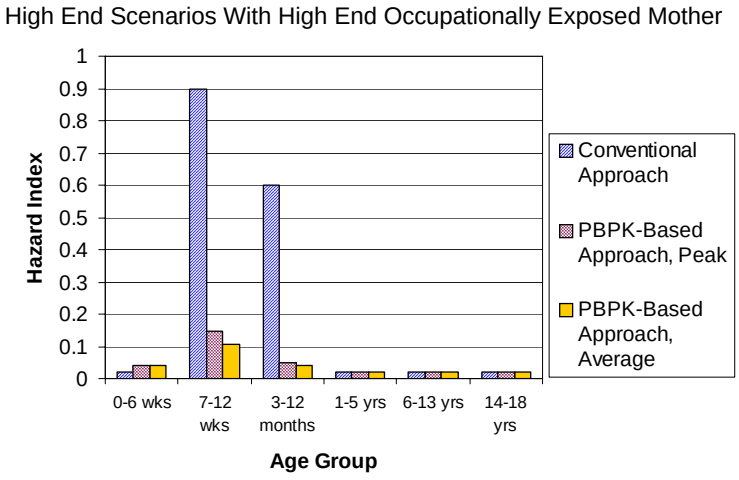
- Infant, 7-12 wks, upper end urban air, human milk from upper end maternal occupational exposure:

Route	Exposure Value (Source in document)	Reference dose or conc.	HQ
Inhalation	0.078 mg/m^3 (Table 7.48, p. 172)	5 mg/m^3	0.016
Ingestion	7.4E-02 mg/kg-d (Table 7.46, p. 169)	0.08 mg/kg-d	0.925
Hazard Index:			0.941

Risk Assessment Results – Administered Dose

- Typical and high-end hazard indices (HIs) for most ages total <=0.02
- Higher HIs for infants breast-fed by occupationally exposed mothers
  - HIs between 0.2 and 0.9 depending on age and mother's exposure assumptions
  - Human milk concentrations from occupationally-exposed mothers modeled using model by Fisher et al. 1997

Risk Assessment Results – Hazard Indices for Chronic Exposures



Administered versus Internal Dose Based Risk Assessment

- Internal dose based risk assessment results in lower HIs compared to administered dose evaluation because:
  - Modeled blood levels reflect distribution of oral and inhalation exposure patterns over the course of the day based on indoor/outdoor activity and breast-feeding patterns
    - Peak blood levels are not as high as would occur following a single bolus oral dose

Risk Assessment Results – Acute Exposure Scenarios

- Highest exposure scenario from "mixed-media" arts scenario for infants
  - Serial use of adhesive and spray glass frosting products over the course of 2 to 3 hours in enclosed space with infant in the same room during and for several hours after
- AEGL-1 (4-hour; 200 ppm) was used as the exposure benchmark
  - Associated peak blood level (~3.5 mg/L) also modeled

Blood Levels in Humans – Acute Neurological Responses

- Benignus et al. (1998) found that blood levels correlated well with changes in neurological responses
- 10% change in choice reaction time at blood levels of about 3 mg/L
  - Similar to AEGL-1 (200 ppm, 4-hour) modeled peak blood toluene level ~ 3.5 mg/L

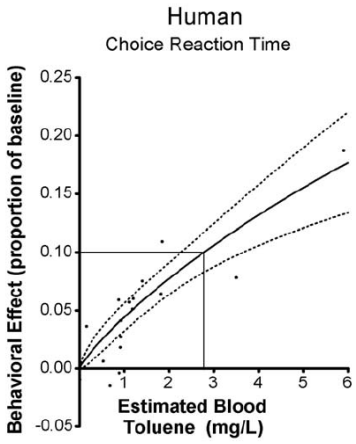
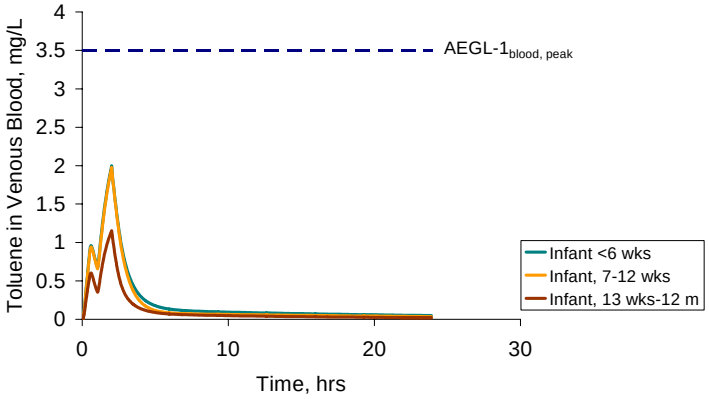


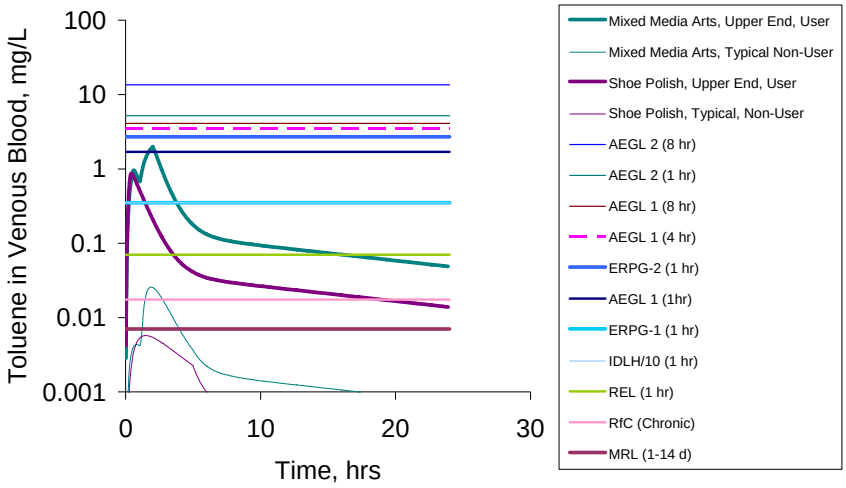
Figure 1 from Bushnell et al. 2006

Comparison of Modeled Blood Levels – Acute Exposure Scenario

(Mixed-Media Arts)



Infrequent Acute Exposures and Exposure Guidelines



Comparison to Available Biomonitoring Data in Children (Sexton et al. 2005)

- Elementary school-aged children (n=60 to 160)
- Four samples during two seasons over two years
- Excellent agreement with estimated and modeled exposures in this analysis
- HIs range from 0.005-0.02 compared to RfC_{Blood} of 17.5 ug/L

	Median (ug/L)	95th percentile (ug/L)
Sexton et al. (2005)	0.10	0.25
	0.08	0.20
	0.11	0.19
	0.17	0.37
VCCEP modeled	0.08-0.11 (typical)	0.31-0.36 (high end)

Conclusions

- Internal dose metric (blood toluene levels) relevant for risk assessment
  - For sensitive endpoints in humans (neurotoxicity)
  - For capturing age-dependent changes in ADME (sensitivities)
  - Probably superior to administered dose for evaluating risks
- PBPK models provide a rational basis for examining the impact of known physiologic and metabolic differences between children and adults

Conclusions *(continued)*

- Risks were assessed using all available health-based benchmarks (RfC, RfD) and age-specific pharmacokinetic models
- Biomonitoring data provide additional confidence in results of modeling, exposure and risk assessment
- Toluene exposures from the environment are associated with HIs considerably less than 0.1

Toluene VCCEP
Data Needs Assessment

TERA Peer Consultation Meeting
November 7-8, 2006

Andrew Jaques,
American Chemistry Council

VCCEP Hazard Data

- Studies are available on toluene for each VCCEP endpoint:
  - √ Acute
  - √ Subchronic
  - √ Genotoxicity (*in vitro* and *in vivo*)
  - √ 2-Gen Reproductive Effects
  - √ Developmental Toxicity
  - √ Immunotoxicity
  - √ ADME
  - √ Neurotoxicity
  - √ Developmental Neurotoxicity
  - √ Chronic
- Considerable human experience and epidemiology data.

VCCEP Hazard Data Needs

- ADME and pharmacokinetic data are available.
- PBPK models are available to address hazards across different routes of exposure and different age ranges.
- No VCCEP toxicology study data needs have been identified.

VCCEP Exposure Data

- Inhalation is the predominant route of exposure.
- Ample peer-reviewed measurements of air concentrations in homes, schools, workplaces, automobiles, and outdoors exist for toluene.

VCCEP Exposure Data Needs

- The risk assessment does not indicate health risks.
- Additional exposure information is not likely to enhance the risk assessment or identify new critical exposures or pathways.
- Toluene is well regulated under a number of environmental and health regulations.
- No further exposure studies are proposed for toluene.

Appendix D

Errata Sheet and Expanded Household Products Database

Response to TERA's QA/QC of exposure calculations comments

The dose values for refueling in Table 7 47 are incorrect – the correct ones are on Table A-14 9 It appears that the cells in the summary table were not updated Table A-14 10 is wrong in the report, the rows don't match up It seems that there was a copy/paste problem from Excel – but the dose values listed there are correct and the ETS numbers in the summary table 7 47 are correct Attached is the correct Table that belongs in A-14 10

Table A-14.10 Summary of ADDs from ETS Toluene Exposure (mg/kg-day)

Exposure Parameter	Units	0-6 weeks old	7-12 weeks old	13 weeks - 12 months old	1-5 year old	6-13 year old	14-18 year old	19-35 year old
C	µg/m3	1 5	1 5	1 5	1 4	1 2	1 1	1 5
ET	hours/day	24	24	24	24	24	24	24
EF	days/year	365	365	365	365	365	365	365
ED	years	0 12	0 12	0 77	5	8	5	17
IR	m3/h	0 19	0 19	0 19	0 31	0 51	0 6	0 47
CF	mg/µg	0 001	0 001	0 001	0 001	0 001	0 001	0 001
AT	days	42	42	281	1825	2920	1825	6205
BW	kg	3 6	5 4	8 4	15 4	35	61	62 4
ABSi	unitless	0 5	0 5	0 5	0 5	0 5	0 5	0 5
Dose	mg/kg-d	9.50E-04	6.33E-04	4.07E-04	3.38E-04	2.10E-04	1.30E-04	1.36E-04

Chemical Information

Chemical Name: Toluene

CAS Registry Number: 000108-88-3

Synonyms: Toluene; Benzene, methyl-; Methane, phenyl-; Methylbenzene; Methylbenzol; Toluol

Information from other National Library of Medicine databases

Health Studies: Human Health Effects from Hazardous Substances Data Bank (HSDB)

Toxicity Information: Search TOXNET

Chemical Information: Search ChemIDplus

Biomedical References: Search PubMed

Products that contain this ingredient

Brand	Category	Form	Percent
Carb Medic Carburetor Choke and Valve Cleaner-08/01/2002	Auto products	liquid	10-20
Valvoline Carburetor And Choke Cleaner	Auto products	liquid	30-35
Rust Oleum Premium Metallic, Brilliant Metal Finish, Matte Aluminum	Auto products	aerosol	45
Gumout Professional Non Flammable Brake Parts Cleaner	Auto products	aerosol	5-30
Champion Carburetor Cleaner	Auto products	aerosol	30 - 35
Dupli Color Engine Paints	Auto products	aerosol	0-12
Trouble Free Choke and Carb Cleaner	Auto products	liquid	
Gumout Professional Non Chlorinated Brake Parts Cleaner	Auto products	aerosol	5-25
Gumout 2 Part Professional Fuel System Cleaner, Step 1	Auto products	liquid	30-40
Champion Sprayon Brake Parts Cleaner	Auto products	aerosol	15 - 20

Rust Curb Fast Dry Gray	Hobby/Craft	aerosol	15 - 20
Rust Curb Fast Dry Royal Blue	Hobby/Craft	aerosol	15 - 20
ProsALL Progalv	Hobby/Craft	aerosol	15 - 20
SprayPAK Enamel Paint-Blue	Hobby/Craft	aerosol	15 - 20
SprayPAK Enamel-Clear	Hobby/Craft	aerosol	10 - 15
SprayPAK Enamel-Gloss White	Hobby/Craft	aerosol	10 - 15
SprayPAK Gray Metal Primer	Hobby/Craft	aerosol	5 - 10
SprayPAK Enamel-Medium Gray	Hobby/Craft	aerosol	15 - 20
SprayPAK Enamel-Off White	Hobby/Craft	aerosol	15 - 20
Champion Sprayon Primer-Red	Hobby/Craft	aerosol	5 - 10
FolkArt Finishes - Aerosol Sanding Sealer, 11 oz.	Hobby/Craft	aerosol	2.0
Liquid Nails Adhesive, Clear, For Small Projects and Repairs-12/03/2001	Hobby/Craft	tube	5-10
Parks Adhesive Remover-09/04/1998	Hobby/Craft	liquid	5-10
Rust Oleum Premium Stops Rust Protective Enamel Spray 7701 Crystal Clear	Hobby/Craft	aerosol	15
Rust Oleum Premium Stops Rust Protective Enamel Spray 7722 Harbor Blue	Hobby/Craft	aerosol	15
Rust Oleum Premium Stops Rust Protective Enamel Spray 7724 Sail Blue	Hobby/Craft	aerosol	10
Rust Oleum Premium Stops Rust Protective Enamel Spray 7729 Teal Gloss	Hobby/Craft	aerosol	15
Rust Oleum Premium Stops Rust Protective Enamel Spray 7733 Dark Hunter Green	Hobby/Craft	aerosol	10
Rust Oleum Premium Stops Rust Protective Enamel Spray 7747 Sunburst Yellow	Hobby/Craft	aerosol	20
Rust Oleum Premium Stops Rust Protective Enamel Spray 7755 Light Olive Green	Hobby/Craft	aerosol	15
Rust Oleum Premium Stops Rust Protective Enamel Spray 7765 Regal Red	Hobby/Craft	aerosol	10
Rust Oleum Premium Stops Rust Protective Enamel Spray 7770 Almond	Hobby/Craft	aerosol	10
Rust Oleum Premium Stops Rust Protective Enamel Spray 7797 Semi Gloss White	Hobby/Craft	aerosol	5
Rust Oleum Premium Stops Rust Protective Enamel Spray 7763 Carnival Red	Hobby/Craft	aerosol	25
Radio Shack PlastiDip Spray, Clear	Hobby/Craft	aerosol	4
Radio Shack PlastiDip Spray, Black	Hobby/Craft	aerosol	4
Radio Shack PlastiDip Spray, Green	Hobby/Craft	aerosol	4
Radio Shack PlastiDip, Red	Hobby/Craft	liquid	14 8
Radio Shack PlastiDip, Black	Hobby/Craft	liquid	14 8
Radio Shack PlastiDip, Blue	Hobby/Craft	liquid	14 8
Rubberize It Rubberized Plastic Coating, Blue	Hobby/Craft	aerosol	
Champion Sprayon Polyurethane	Hobby/Craft	aerosol	1 - 5
Champion Sprayon Enamel-Pink	Hobby/Craft	aerosol	15 - 20
Champion Sprayon Metallic-24kt Gold	Hobby/Craft	aerosol	30 - 35

Krylon Interior/Exterior Satin Paint, Ivory	Home inside	aerosol	42
Carpenters Goop Contact Adhesive and Sealant, Original Formula	Home inside	tube	37
Champion Polish Brass	Home inside	aerosol	30 - 35
SprayPAK Enamel Paint -Red	Home maintenance	aerosol	15 - 20
SprayPAK Enamel Paint-Yellow	Home maintenance	aerosol	10 - 15
Parks Liquid Deglosser-09/04/1998	Home maintenance	liquid	<25
Rust Oleum Premium Satin Aerosol 7742 Summer Straw	Home maintenance	aerosol	10
Rust Oleum Premium Satin Aerosol 7744 Cornmeal	Home maintenance	aerosol	5
Rust Oleum Premium Satin Aerosol 7791 Satin White	Home maintenance	aerosol	5
Liquid Nails Adhesive, Subfloor and Decks, Exterior & Interior	Home maintenance	caulk tube	5-10
Rust Oleum Professional Inverted Marking Paint, Caution Blue	Home maintenance	aerosol	20 0
Zinc It Electric Grade Lubricant	Home maintenance	aerosol	4 0
PL 400 Construction Adhesive	Home maintenance	semi-solid	5-10
Lexel Caulk/Weatherproofing	Home maintenance	paste	9 61
PL 185 Wallboard Adhesive	Home maintenance	semi-solid	
Savogran Strypeeze Paint/Varnish Remover	Home maintenance	liquid	>35
Champion Sprayon Epoxy Paint-Almond	Home maintenance	aerosol	5-10
Colorworks from Krylon Paint	Home maintenance	aerosol	21-58
Colorworks from Krylon Lacquer Spray	Home maintenance	aerosol	0-3
Water White Rubbed Effect Clear Lacquer (Professional)	Home maintenance	aerosol	19 48
Color All Spray Enamel	Home maintenance	aerosol	30-58
Parks Brush Cleaner	Home maintenance	liquid	<40
Parks Furniture Refinisher	Home maintenance	liquid	15-35
OSI Pro Series Formula #48 Construction Adhesive-10/18/2002	Home maintenance	cartridge	5-10
Parks Liquid Strip	Home maintenance	liquid	<40
OSI Pro Series RT 600 Roof Tile Adhesive-06/02/2003	Home maintenance	cartridge	trace
Rust Oleum Metallic Topcoats	Home maintenance	aerosol	20-60
Zinc-It Instant Cold Galvanize (aerosol)-12/30/2003	Home maintenance	aerosol	10-30
Zinc It Instant Cold Galvanize (aerosol)	Home maintenance	aerosol	10-30
Amazing Goop All Purpose Adhesive and Sealant-03/24/2003	Home maintenance	tube	37
Rust Oleum Bright Coat Metallic Finish, Chrome	Home maintenance	aerosol	30.0
Rust Oleum Painters Touch, Frosted Glass Finish	Home maintenance	aerosol	50.0
Minwax Wood Finish Aerosol, Golden Oak	Home maintenance	aerosol	1
Minwax Wood Finish Aerosol, Special Walnut	Home maintenance	aerosol	1
Paint & Varnish Remover No. 2600, Aerosol	Home maintenance	aerosol	
Minwax Wood Finish Aerosol, Golden Pecan	Home maintenance	aerosol	1
Minwax Wood Finish Aerosol, Dark Walnut	Home maintenance	aerosol	1
Plumbers Goop Contact Adhesive and Sealant, Original Formula	Home maintenance	tube	37
OSI Pro Series Formula #48 Construction Adhesive	Home maintenance	cartridge	5-10

Minwax Wood Finish Aerosol, Red Oak	Home maintenance	aerosol	1
Outdoor Goop Contact Adhesive and Sealant	Home maintenance	tube	37
OSI Pro Series SF 450 Heavy Duty Subfloor Adhesive	Home maintenance	cartridge	5-10
PL Household Adhesive	Home maintenance	tube	5-10
OSI Pro Series RT 600 Roof Tile Adhesive	Home maintenance	cartridge	5-10
PL Mirror Mastic Adhesive	Home maintenance	cartridge	5-10
Champion Cold Galvanize	Home maintenance	aerosol	15-20
PL Landscape Block & Paver Adhesive	Landscaping/Yard	caulk tube	5-10
Rust Oleum Professional Inverted Striping Paint, Yellow	Landscaping/Yard	aerosol	25 0
Lacquer Spraying, Clear, TT-L-58E	Personal care/use	spray	
Bonide Fung-onil Lawn Disease Control	Pesticides	liquid	

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