Acute Exposure Guideline Levels for Selected Airborne Chemicals, Volume 9

Committee on Acute Exposure Guideline Levels; Committee on Toxicology; National Research Council

ISBN: 0-309-15945-8, 462 pages, 6 x 9, (2010)

Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 9

Committee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 FIFTH STREET, NW WASHINGTON, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This project was supported by Contract No. W81K04-06-D-0023 and EP-W-09-007 between the National Academy of Sciences and the U.S. Department of Defense and the U.S. Environmental Protection Agency. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

International Standard Book Number-13: 978-0-309-15944-9
International Standard Book Number-10: 0-309-15944-X

Additional copies of this report are available from

The National Academies Press
500 Fifth Street, NW
Box 285
Washington, DC 20055

800-624-6242
202-334-3313 (in the Washington metropolitan area)
http://www.nap.edu

Printed in the United States of America

THE NATIONAL ACADEMIES

Advisers to the Nation on Science, Engineering, and Medicine

The **National Academy of Sciences** is a private, nonprofit, self-perpetuating society of distinguished scholars engaged in scientific and engineering research, dedicated to the furtherance of science and technology and to their use for the general welfare. Upon the authority of the charter granted to it by the Congress in 1863, the Academy has a mandate that requires it to advise the federal government on scientific and technical matters. Dr. Ralph J. Cicerone is president of the National Academy of Sciences.

The **National Academy of Engineering** was established in 1964, under the charter of the National Academy of Sciences, as a parallel organization of outstanding engineers. It is autonomous in its administration and in the selection of its members, sharing with the National Academy of Sciences the responsibility for advising the federal government. The National Academy of Engineering also sponsors engineering programs aimed at meeting national needs, encourages education and research, and recognizes the superior achievements of engineers. Dr. Charles M. Vest is president of the National Academy of Engineering.

The **Institute of Medicine** was established in 1970 by the National Academy of Sciences to secure the services of eminent members of appropriate professions in the examination of policy matters pertaining to the health of the public. The Institute acts under the responsibility given to the National Academy of Sciences by its congressional charter to be an adviser to the federal government and, upon its own initiative, to identify issues of medical care, research, and education. Dr. Harvey V. Fineberg is president of the Institute of Medicine.

The **National Research Council** was organized by the National Academy of Sciences in 1916 to associate the broad community of science and technology with the Academy's purposes of furthering knowledge and advising the federal government. Functioning in accordance with general policies determined by the Academy, the Council has become the principal operating agency of both the National Academy of Sciences and the National Academy of Engineering in providing services to the government, the public, and the scientific and engineering communities. The Council is administered jointly by both Academies and the Institute of Medicine. Dr. Ralph J. Cicerone and Dr. Charles M. Vest are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

COMMITTEE ON ACUTE EXPOSURE GUIDELINE LEVELS

Members

DONALD E. GARDNER *(Chair)*, Inhalation Toxicology Associates, Savannah, GA
EDWARD C. BISHOP, HDR Inc., Omaha, NE
RAKESH DIXIT, MedImmune/AstraZeneca Biologics, Inc., Gaithersburg, MD
JEFFREY W. FISHER, University of Georgia, Athens, GA
DAVID P. KELLY, Dupont Company, Newark, DE
DAVID A. MACYS, U.S. Department of the Navy (retired), Oak Harbor, WA
FRANZ OESCH, University of Mainz, Mainz, Germany
RICHARD B. SCHLESINGER, Pace University, New York, NY
ROBERT SNYDER, Rutgers University, Piscataway, NJ
JOHN A. THOMAS, Indiana University School of Medicine, Indianapolis, IN
FREDERIK A. DE WOLFF, Leiden University Medical Center (retired), Leiden, The Netherlands

Staff

RAYMOND WASSEL, Senior Program Officer for Environmental Studies
KEEGAN SAWYER, Associate Program Officer
RUTH CROSSGROVE, Senior Editor
MIRSADA KARALIC-LONCAREVIC, Manager, Technical Information Center
RADIAH ROSE, Manager, Editorial Projects
ORIN LUKE, Senior Program Assistant

Sponsors

U.S. DEPARTMENT OF DEFENSE
U.S. ENVIRONMENTAL PROTECTION AGENCY

COMMITTEE ON TOXICOLOGY

Members

GARY P. CARLSON (*Chair*), Purdue University, West Lafayette, IN
LAWRENCE S. BETTS, Eastern Virginia Medical School, Norfolk
EDWARD C. BISHOP, HDR Engineering, Inc., Omaha, NE
JAMES V. BRUCKNER, University of Georgia, Athens
MARION F. EHRICH, Virginia Polytechnic Institute and State University, Blacksburg
SIDNEY GREEN, Howard University, Washington, DC
WILLIAM E. HALPERIN, UMDNJ–New Jersey Medical School, Newark
MERYL H. KAROL, University of Pittsburgh, Pittsburgh, PA
JAMES N. MCDOUGAL, Wright State University School of Medicine, Dayton, OH
ROGER G. MCINTOSH, Science Applications International Corporation, Abingdon, MD
JOYCE TSUJI, Exponent, Inc., Bellevue, WA
GERALD N. WOGAN, Massachusetts Institute of Technology, Cambridge

Staff

SUSAN N.J. MARTEL, Senior Program Officer for Toxicology
ELLEN K. MANTUS, Senior Program Officer for Risk Analysis
RAYMOND A. WASSEL, Senior Program Officer for Environmental Studies
EILEEN N. ABT, Senior Program Officer
KEEGAN SAWYER, Associate Program Officer
RUTH E. CROSSGROVE, Senior Editor
MIRSADA KARALIC-LONCAREVIC, Manager, Technical Information Center
RADIAH ROSE, Manager, Editorial Projects
TAMARA DAWSON, Program Associate

[1]This study was planned, overseen, and supported by the Board on Environmental Studies and Toxicology.

OTHER REPORTS OF THE
BOARD ON ENVIRONMENTAL STUDIES AND TOXICOLOGY

Contaminated Water Supplies at Camp Lejeune—Assessing Potential Health Effects (2009)
Review of the Federal Strategy for Nanotechnology-Related Environmental, Health, and Safety Research (2009)
Science and Decisions: Advancing Risk Assessment (2009)
Phthalates and Cumulative Risk Assessment: The Tasks Ahead (2008)
Estimating Mortality Risk Reduction and Economic Benefits from Controlling Ozone Air Pollution (2008)
Respiratory Diseases Research at NIOSH (2008)
Evaluating Research Efficiency in the U.S. Environmental Protection Agency (2008)
Hydrology, Ecology, and Fishes of the Klamath River Basin (2008)
Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment (2007)
Models in Environmental Regulatory Decision Making (2007)
Toxicity Testing in the Twenty-first Century: A Vision and a Strategy (2007)
Sediment Dredging at Superfund Megasites: Assessing the Effectiveness (2007)
Environmental Impacts of Wind-Energy Projects (2007)
Scientific Review of the Proposed Risk Assessment Bulletin from the Office of Management and Budget (2007)
Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues (2006)
New Source Review for Stationary Sources of Air Pollution (2006)
Human Biomonitoring for Environmental Chemicals (2006)
Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment (2006)
Fluoride in Drinking Water: A Scientific Review of EPA's Standards (2006)
State and Federal Standards for Mobile-Source Emissions (2006)
Superfund and Mining Megasites—Lessons from the Coeur d'Alene River Basin (2005)
Health Implications of Perchlorate Ingestion (2005)
Air Quality Management in the United States (2004)
Endangered and Threatened Species of the Platte River (2004)
Atlantic Salmon in Maine (2004)
Endangered and Threatened Fishes in the Klamath River Basin (2004)
Cumulative Environmental Effects of Alaska North Slope Oil and Gas Development (2003)
Estimating the Public Health Benefits of Proposed Air Pollution Regulations (2002)
Biosolids Applied to Land: Advancing Standards and Practices (2002)
The Airliner Cabin Environment and Health of Passengers and Crew (2002)
Arsenic in Drinking Water: 2001 Update (2001)
Evaluating Vehicle Emissions Inspection and Maintenance Programs (2001)
Compensating for Wetland Losses Under the Clean Water Act (2001)
A Risk-Management Strategy for PCB-Contaminated Sediments (2001)
Acute Exposure Guideline Levels for Selected Airborne Chemicals (seven volumes, 2000-2009)
Toxicological Effects of Methylmercury (2000)
Strengthening Science at the U.S. Environmental Protection Agency (2000)

Scientific Frontiers in Developmental Toxicology and Risk Assessment (2000)
Ecological Indicators for the Nation (2000)
Waste Incineration and Public Health (2000)
Hormonally Active Agents in the Environment (1999)
Research Priorities for Airborne Particulate Matter (four volumes, 1998-2004)
The National Research Council's Committee on Toxicology: The First 50 Years (1997)
Carcinogens and Anticarcinogens in the Human Diet (1996)
Upstream: Salmon and Society in the Pacific Northwest (1996)
Science and the Endangered Species Act (1995)
Wetlands: Characteristics and Boundaries (1995)
Biologic Markers (five volumes, 1989-1995)
Science and Judgment in Risk Assessment (1994)
Pesticides in the Diets of Infants and Children (1993)
Dolphins and the Tuna Industry (1992)
Science and the National Parks (1992)
Human Exposure Assessment for Airborne Pollutants (1991)
Rethinking the Ozone Problem in Urban and Regional Air Pollution (1991)
Decline of the Sea Turtles (1990)

Copies of these reports may be ordered from the National Academies Press
(800) 624-6242 or (202) 334-3313
www.nap.edu

OTHER REPORTS OF THE COMMITTEE ON TOXICOLOGY

Review of the Department of Defense Enhanced Particulate Matter Surveillance Program Report (2010)
Evaluation of the Health and Safety Risks of the New USAMRIID High-Containment Facilities at Fort Detrick, Maryland (2010)
Combined Exposures to Hydrogen Cyanide and Carbon Monoxide in Army Operations: Final Report (2008)
Managing Health Effects of Beryllium Exposure (2008)
Review of Toxicologic and Radiologic Risks to Military Personnel from Exposures to Depleted Uranium (2008)
Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Volume 1 (2007), Volume 2 (2008)
Review of the Department of Defense Research Program on Low-Level Exposures to Chemical Warfare Agents (2005)
Review of the Army's Technical Guides on Assessing and Managing Chemical Hazards to Deployed Personnel (2004)
Spacecraft Water Exposure Guidelines for Selected Contaminants, Volume 1 (2004), Volume 2 (2007), Volume 3 (2008)
Toxicologic Assessment of Jet-Propulsion Fuel 8 (2003)
Review of Submarine Escape Action Levels for Selected Chemicals (2002)
Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (2001)
Evaluating Chemical and Other Agent Exposures for Reproductive and Developmental Toxicity (2001)
Acute Exposure Guideline Levels for Selected Airborne Contaminants, Volume 1 (2000), Volume 2 (2002), Volume 3 (2003), Volume 4 (2004), Volume 5 (2007), Volume 6 (2008), Volume 7 (2009), Volume 8 (2009)
Review of the U.S. Navy's Human Health Risk Assessment of the Naval Air Facility at Atsugi, Japan (2000)
Methods for Developing Spacecraft Water Exposure Guidelines (2000)
Review of the U.S. Navy Environmental Health Center's Health-Hazard Assessment Process (2000)
Review of the U.S. Navy's Exposure Standard for Manufactured Vitreous Fibers (2000)
Re-Evaluation of Drinking-Water Guidelines for Diisopropyl Methylphosphonate (2000)
Submarine Exposure Guidance Levels for Selected Hydrofluorocarbons: HFC-236fa, HFC-23, and HFC-404a (2000)
Review of the U.S. Army's Health Risk Assessments for Oral Exposure to Six Chemical-Warfare Agents (1999)
Toxicity of Military Smokes and Obscurants, Volume 1(1997), Volume 2 (1999), Volume 3 (1999)
Assessment of Exposure-Response Functions for Rocket-Emission Toxicants (1998)
Toxicity of Alternatives to Chlorofluorocarbons: HFC-134a and HCFC-123 (1996)
Permissible Exposure Levels for Selected Military Fuel Vapors (1996)
Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Volume 1 (1994), Volume 2 (1996), Volume 3 (1996), Volume 4 (2000), Volume 5 (2008)

Preface

Extremely hazardous substances (EHSs)[2] can be released accidentally as a result of chemical spills, industrial explosions, fires, or accidents involving railroad cars and trucks transporting EHSs. Workers and residents in communities surrounding industrial facilities where EHSs are manufactured, used, or stored and in communities along the nation's railways and highways are potentially at risk of being exposed to airborne EHSs during accidental releases or intentional releases by terrorists. Pursuant to the Superfund Amendments and Reauthorization Act of 1986, the U.S. Environmental Protection Agency (EPA) has identified approximately 400 EHSs on the basis of acute lethality data in rodents.

As part of its efforts to develop acute exposure guideline levels for EHSs, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR) in 1991 requested that the National Research Council (NRC) develop guidelines for establishing such levels. In response to that request, the NRC published *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* in 1993. Subsequently, *Standard Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Substances* was published in 2001, providing updated procedures, methodologies, and other guidelines used by the National Advisory Committee (NAC) on Acute Exposure Guideline Levels for Hazardous Substances and the Committee on Acute Exposure Guideline Levels (AEGLs) in developing the AEGL values.

Using the 1993 and 2001 NRC guidelines reports, the NAC—consisting of members from EPA, the Department of Defense (DOD), the Department of Energy (DOE), the Department of Transportation (DOT), other federal and state governments, the chemical industry, academia, and other organizations from the private sector—has developed AEGLs for approximately 200 EHSs.

In 1998, EPA and DOD requested that the NRC independently review the AEGLs developed by NAC. In response to that request, the NRC organized within its Committee on Toxicology (COT) the Committee on Acute Exposure Guideline Levels, which prepared this report. This report is the ninth volume in

[2]As defined pursuant to the Superfund Amendments and Reauthorization Act of 1986.

the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*. It reviews the AEGLs for bromine, ethylene oxide, furan, hydrogen sulfide, propylene oxide, and xylenes for scientific accuracy, completeness, and consistency with the NRC guideline reports. It also includes a chapter addressing the use of physiologically based pharmacokinetic (PBPK) models to support the derivation of AEGLs.

The committee's review of the AEGL documents involved both oral and written presentations to the committee by the NAC authors of the documents. The committee examined the draft documents and provided comments and recommendations for how they could be improved in a series of interim reports. The authors revised the draft AEGL documents based on the advice in the interim reports and presented them for reexamination by the committee as many times as necessary until the committee was satisfied that the AEGLs were scientifically justified and consistent with the 1993 and 2001 NRC guideline reports. After these determinations have been made for an AEGL document, it is published as an appendix in a volume such as this one.

The nine interim reports of the committee that led to this report were reviewed in draft form by individuals selected for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of the nine committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for bromine (twelfth and fifteenth interim reports, 2005 and 2008, respectively), ethylene oxide (tenth and fifteenth interim reports, 2004 and 2008, respectively), furan (sixth, eighth, and fifteenth interim reports, 2001, 2002, and 2008, respectively), hydrogen sulfide (third, sixth, seventh, eighth, and ninth interim reports, 2000, 2001, 2002, 2002, and 2003, respectively), propylene oxide (tenth interim report, 2004), xylenes (twelfth and fourteenth interim reports, 2005 and 2006, respectively), and the use of PBPK models to support the derivation of AEGLs (fifteenth interim report, 2008): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), Rakesh Dixit (MedImmune/AstraZeneca Biologics, before he became a member of the committee), David Gaylor (Gaylor and Associates, LLC), Sidney Green (Howard University), A. Wallace Hayes (Harvard School of Public Health), Sam Kacew (University of Ottawa), Nancy Kerkvliet (Oregon State University), Florence K. Kinoshita (Hercules Incorporated [retired]), Kenneth Poirier (Toxicology Excellence for Risk Assessment),Charles R. Reinhardt (DuPont Haskell Laboratory [retired]), and Bernard M. Wagner (New York University Medical Center [retired]).

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of this volume before its release. The review of the third interim report, completed in 2000, was overseen by Mary Vore, University of Kentucky Medical Center. The reviews of the sixth interim report (2001), seventh interim report (2002), fourteenth interim report (2006), and fifteenth interim report (2008) were overseen by Robert Goyer, University of Western Ontario (retired). The reviews of the eighth interim report (2002) and tenth interim report (2004) were overseen by David H. Moore, Battelle Memorial Institute. The review of the ninth interim report (2003) was overseen by Judith A. Graham, American Chemistry Council (retired). The review of the twelfth interim report (2005) was overseen by David W. Gaylor, Gaylor and Associates, LLC. Appointed by the NRC, they were responsible for making certain that an independent examination of the interim reports was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

The committee gratefully acknowledges the valuable assistance provided by the following persons: Ernest Falke, Marquea D. King, Iris A. Camacho, and Paul Tobin (all from EPA); and George Rusch (Honeywell, Inc.). The committee also acknowledges Raymond Wassel and Keegan Sawyer, the project directors for their work this project. Other staff members who contributed to this effort are James J. Reisa (director of the Board on Environmental Studies and Toxicology), Susan Martel (senior program officer for toxicology), Ruth Crossgrove (senior editor), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), Orin Luke (senior program assistant), and Tamara Dawson (program associate). Finally, I would like to thank all members of the committee for their expertise and dedicated effort throughout the development of this report.

Donald E. Gardner, *Chair*
Committee on Acute Exposure
Guideline Levels

Contents

Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 9

National Research Council Committee Review of Acute Exposure Guideline Levels of Selected Airborne Chemicals

This report is the ninth volume in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals*.

In the Bhopal disaster of 1984, approximately 2,000 residents living near a chemical plant were killed and 20,000 more suffered irreversible damage to their eyes and lungs following accidental release of methyl isocyanate. The toll was particularly high because the community had little idea what chemicals were being used at the plant, how dangerous they might be, or what steps to take in an emergency. This tragedy served to focus international attention on the need for governments to identify hazardous substances and to assist local communities in planning how to deal with emergency exposures.

In the United States, the Superfund Amendments and Reauthorization Act (SARA) of 1986 required that the U.S. Environmental Protection Agency (EPA) identify extremely hazardous substances (EHSs) and, in cooperation with the Federal Emergency Management Agency and the U.S. Department of Transportation, assist local emergency planning committees (LEPCs) by providing guidance for conducting health hazard assessments for the development of emergency response plans for sites where EHSs are produced, stored, transported, or used. SARA also required that the Agency for Toxic Substances and Disease Registry (ATSDR) determine whether chemical substances identified at hazardous waste sites or in the environment present a public health concern.

As a first step in assisting the LEPCs, EPA identified approximately 400 EHSs largely on the basis of their immediately dangerous to life and health values, developed by the National Institute for Occupational Safety or Health. Although several public and private groups, such as the Occupational Safety and Health Administration and the American Conference of Governmental Industrial Hygienists, have established exposure limits for some substances and some exposures (e.g., workplace or ambient air quality), these limits are not easily or directly translated into emergency exposure limits for exposures at high levels

but of short duration, usually less than 1 hour (h), and only once in a lifetime for the general population, which includes infants (from birth to 3 years of age), children, the elderly, and persons with diseases, such as asthma or heart disease.

The National Research Council (NRC) Committee on Toxicology (COT) has published many reports on emergency exposure guidance levels and spacecraft maximum allowable concentrations for chemicals used by the U.S. Department of Defense (DOD) and the National Aeronautics and Space Administration (NASA) (NRC 1968, 1972, 1984a,b,c,d, 1985a,b, 1986a, 1987, 1988, 1994, 1996a,b, 2000a, 2002a, 2007a, 2008a). COT has also published guidelines for developing emergency exposure guidance levels for military personnel and for astronauts (NRC 1986b, 1992, 2000b). Because of COT's experience in recommending emergency exposure levels for short-term exposures, in 1991 EPA and ATSDR requested that COT develop criteria and methods for developing emergency exposure levels for EHSs for the general population. In response to that request, the NRC assigned this project to the COT Subcommittee on Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. The report of that subcommittee, *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993), provides step-by-step guidance for setting emergency exposure levels for EHSs. Guidance is given on what data are needed, what data are available, how to evaluate the data, and how to present the results.

In November 1995, the National Advisory Committee (NAC)[1] for Acute Exposure Guideline Levels for Hazardous Substances was established to identify, review, and interpret relevant toxicologic and other scientific data and to develop acute exposure guideline levels (AEGLs) for high-priority, acutely toxic chemicals. The NRC's previous name for acute exposure levels—community emergency exposure levels (CEELs)—was replaced by the term AEGLs to reflect the broad application of these values to planning, response, and prevention in the community, the workplace, transportation, the military, and the remediation of Superfund sites.

AEGLs represent threshold exposure limits (exposure levels below which adverse health effects are not likely to occur) for the general public and are applicable to emergency exposures ranging from 10 minutes (min) to 8 h. Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 min, 30 min, 1 h, 4 h, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm [parts per million] or mg/m^3 [milligrams per cubic meter]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling and are transient and reversible

[1]NAC is composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. The NAC roster is shown on page 9.

upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death.

Airborne concentrations below AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic nonsensory adverse effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY OF REPORT ON GUIDELINES FOR DEVELOPING AEGLS

As described in *Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances* (NRC 1993) and the NRC guidelines report *Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals* (NRC 2001a), the first step in establishing AEGLs for a chemical is to collect and review all relevant published and unpublished information. Various types of evidence are assessed in establishing AEGL values for a chemical. These include information from (1) chemical-physical characterizations, (2) structure-activity relationships, (3) in vitro toxicity studies, (4) animal toxicity studies, (5) controlled human studies, (6) observations of humans involved in chemical accidents, and (7) epidemiologic studies. Toxicity data from human studies are most applicable and are used when available in preference to data from animal studies and in vitro studies. Toxicity data from inhalation exposures are most useful for setting AEGLs for airborne chemicals because inhalation is the most likely route of exposure and because extrapolation of data from other routes would lead to additional uncertainty in the AEGL estimate.

For most chemicals, actual human toxicity data are not available or critical information on exposure is lacking, so toxicity data from studies conducted in laboratory animals are extrapolated to estimate the potential toxicity in humans. Such extrapolation requires experienced scientific judgment. The toxicity data

for animal species most representative of humans in terms of pharmacodynamic and pharmacokinetic properties are used for determining AEGLs. If data are not available on the species that best represents humans, data from the most sensitive animal species are used. Uncertainty factors are commonly used when animal data are used to estimate risk levels for humans. The magnitude of uncertainty factors depends on the quality of the animal data used to determine the no-observed-adverse-effect level (NOAEL) and the mode of action of the substance in question. When available, pharmacokinetic data on tissue doses are considered for interspecies extrapolation.

For substances that affect several organ systems or have multiple effects, all end points (including reproductive [in both genders], developmental, neurotoxic, respiratory, and other organ-related effects) are evaluated, the most important or most sensitive effect receiving the greatest attention. For carcinogenic chemicals, excess carcinogenic risk is estimated, and the AEGLs corresponding to carcinogenic risks of 1 in 10,000 (1×10^{-4}), 1 in 100,000 (1×10^{-5}), and 1 in 1,000,000 (1×10^{-6}) exposed persons are estimated.

REVIEW OF AEGL REPORTS

As NAC began developing chemical-specific AEGL reports, EPA and DOD asked the NRC to review independently the NAC reports for their scientific validity, completeness, and consistency with the NRC guideline reports (NRC 1993, 2001a). The NRC assigned this project to the COT Committee on Acute Exposure Guideline Levels. The committee has expertise in toxicology, epidemiology, occupational health, pharmacology, medicine, pharmacokinetics, industrial hygiene, and risk assessment.

The AEGL draft reports are initially prepared by ad hoc AEGL development teams consisting of a chemical manager, two chemical reviewers, and a staff scientist of the NAC contractor—Oak Ridge National Laboratory. The draft documents are then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents are approved by NAC, they are published in the *Federal Register* for public comment. The reports are then revised by NAC in response to the public comments, elevated from "proposed" to "interim" status, and sent to the NRC Committee on Acute Exposure Guideline Levels for final evaluation.

The NRC committee's review of the AEGL reports prepared by NAC and its contractors involves oral and written presentations to the committee by the authors of the reports. The NRC committee provides advice and recommendations for revisions to ensure scientific validity and consistency with the NRC guideline reports (NRC 1993, 2001a). The revised reports are presented at subsequent meetings until the subcommittee is satisfied with the reviews.

Because of the enormous amount of data presented in AEGL reports, the NRC committee cannot verify all of the data used by NAC. The NRC committee relies on NAC for the accuracy and completeness of the toxicity data cited in the

AEGL reports. Thus far, the committee has prepared seven reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010). This report is the ninth volume in that series. AEGL documents for bromine, ethylene oxide, furan, hydrogen sulfide, propylene oxide, and xylenes are each published as an appendix in this report. This volume also contains a chapter on the use of physiologically based pharmacokinetic models to support the derivation of AEGLs. The committee concludes that the AEGLs developed in these appendixes are scientifically valid conclusions based on the data reviewed by NAC and are consistent with the NRC guideline reports. AEGL reports for additional chemicals will be presented in subsequent volumes.

REFERENCES

NRC (National Research Council). 1968. Atmospheric Contaminants in Spacecraft. Washington, DC: National Academy of Sciences.

NRC (National Research Council). 1972. Atmospheric Contaminants in Manned Spacecraft. Washington, DC: National Academy of Sciences.

NRC (National Research Council). 1984a. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 1984b. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 2. Washington, DC: National Academy Press.

NRC (National Research Council). 1984c. Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 3. Washington, DC: National Academy Press.

NRC (National Research Council). 1984d. Toxicity Testing: Strategies to Determine Needs and Priorities. Washington, DC: National Academy Press.

NRC (National Research Council). 1985a. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

NRC (National Research Council). 1985b. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 5. Washington, DC: National Academy Press.

NRC (National Research Council). 1986a. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 6. Washington, DC: National Academy Press.

NRC (National Research Council). 1986b. Criteria and Methods for Preparing Emergency Exposure Guidance Level (EEGL), Short-Term Public Emergency Guidance Level (SPEGL), and Continuous Exposure Guidance level (CEGL) Documents. Washington, DC: National Academy Press.

NRC (National Research Council). 1987. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 7. Washington, DC: National Academy Press.

NRC (National Research Council). 1988. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 8. Washington, DC: National Academy Press.

NRC (National Research Council). 1992. Guidelines for Developing Spacecraft Maximum Allowable Concentrations for Space Station Contaminants. Washington, DC: National Academy Press.

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 1994. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 1996a. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 2. Washington, DC: National Academy Press.

NRC (National Research Council). 1996b. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 3. Washington, DC: National Academy Press.

NRC (National Research Council). 2000a. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 4. Washington, DC: National Academy Press.

NRC (National Research Council). 2000b. Methods for Developing Spacecraft Water Exposure Guidelines. Washington, DC: National Academy Press.

NRC (National Research Council). 2001a. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NRC (National Research Council) 2001b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council) 2002a. Review of Submarine Escape Action Levels for Selected Chemicals. Washington, DC: The National Academies Press.

NRC (National Research Council) 2002b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol 2. Washington, DC: The National Academies Press.

NRC (National Research Council) 2003. Acute Exposure Guideline Levels for Selected Airborne Chemical, Vol. 3. Washington, DC: The National Academies Press.

NRC (National Research Council) 2004. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 4. Washington, DC: The National Academies Press.

NRC (National Research Council) 2007a. Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Vol. 1. Washington, DC: The National Academies Press.

NRC (National Research Council) 2007b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 5. Washington, DC: The National Academies Press.

NRC (National Research Council) 2008a. Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Vol. 2. Washington, DC: The National Academies Press.

NRC (National Research Council) 2008b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 6. Washington, DC: The National Academies Press.

NRC (National Research Council) 2009. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 7. Washington, DC: The National Academies Press.

NRC (National Research Council) 2010. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 8. Washington, DC: The National Academies Press.

Roster of the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

Committee Members

Henry Anderson
Wisconsin Department of Health
Madison, WI

Marc Baril
Institut de Recherche
Robert-Sauvé en santé et sécurité du
travail (IRSST) Government of Canada

Lynn Beasley
U.S. Environmental Protection Agency
Washington, DC

Alan Becker
College of Health and Human Services
Missouri State University
Springfield, MO

Robert Benson
U.S. Environmental Protection Agency
Region VIII
Denver, CO

Edward Bernas
AFL-CIO
Homewood, IL

Iris Camacho
U.S. Environmental Protection Agency
Washington, DC

George Cushmac
Office of Hazardous Materials Safety
U.S. Department of Transportation
Washington, DC

Richard Erickson
U.S. Navy
Groton, CT

Neeraja Erranguntla
Texas Commission on
Environmental Quality
Austin, TX

David Freshwater
U. S. Department of Energy
Washington, DC

Ralph Gingell
Shell Health Services
Houston, TX

John P. Hinz
U.S. Air Force
Brooks Air Force Base, TX

James Holler
Agency for Toxic Substances and
Disease Registry
Atlanta, GA

Clarion E. Johnson
Exxon Mobil Corporation
Fairfax, VA

Glenn Leach
U.S. Army Center for Health Promotion
and Preventive Medicine Toxicity
Evaluation
Aberdeen Proving Grounds, MD

Richard W. Niemeier
National Institute for Occupational
Safety and Health
Cincinnati, OH

Mattias Oberg
Swedish Institute of Environmental
Medicine (Karolinska Institutet)
Stockholm, Sweden

Susan Ripple
The Dow Chemical Company
Midland, Michigan

George Rusch
Chair, NAC/AEGL Committee
Department of Toxicology and
Risk Assessment
Honeywell, Inc.
Morristown, NJ

Daniel Sudakin
Oregon State University
Corvallis, OR

Marcel T. M. van Raaij
National Institute of Public Health and
Environment (RIVM)
Bilthoven, The Netherlands

George Woodall
U.S. Environmental Protection Agency
Research Triangle Park, NC

Alan Woolf
Children's Hospital
Boston, MA

Oak Ridge National Laboratory Staff

Cheryl Bast
Oak Ridge National Laboratory
Oak Ridge, TN

Kowetha Davidson
Oak Ridge National Laboratory
Oak Ridge, TN

Sylvia Talmage
Oak Ridge National Laboratory
Oak Ridge, TN

Claudia Troxel
Oak Ridge National Laboratory
Oak Ridge, TN

National Advisory Committee Staff

Paul S. Tobin
Designated Federal Officer, AEGL Program
U.S. Environmental Protection Agency
Washington, DC

Ernest Falke
U.S. Environmental Protection Agency
Washington, DC

Iris A. Camacho
U.S. Environmental Protection Agency
Washington, DC

Sharon Frazier
U.S. Environmental Protection Agency
Washington, DC

Appendixes

6

Xylenes[1]

Acute Exposure Guideline Levels

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P.L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review, and interpret relevant toxicologic and other scientific data and develop AEGLs for high-priority, acutely toxic chemicals. AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes (min) to 8 hours (h). Three levels—AEGL-1, AEGL-2, and AEGL-3—are developed for each of five exposure periods (10 and 30 min and 1, 4, and 8 h) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million [ppm] or milligrams per cubic meter [mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory

[1]This document was prepared by the AEGL Development Team composed of Claudia Troxel (Oak Ridge National Laboratory) and Chemical Manager Loren Koller (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances). The NAC reviewed and revised the document and AEGLs as deemed necessary. Both the document and the AEGL values were then reviewed by the National Research Council (NRC) Committee on Acute Exposure Guideline Levels. The NRC committee has concluded that the AEGLs developed in this document are scientifically valid conclusions based on the data reviewed by the NRC and are consistent with the NRC guideline reports (NRC 1993, 2001).

effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGLs represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

SUMMARY

Xylene is found in a number of consumer products, including solvents, paints and coatings, and as a blend in gasoline. Mixed xylenes are composed of three isomers: *m*-xylene, *o*-xylene, and *p*-xylene, with the *m*-isomer predominating. Ethylbenzene is also present in the technical product formulation. Absorbed xylene is rapidly metabolized and is excreted almost exclusively in the urine as methylhippuric acid isomers in humans and as methylhippuric acid isomers and toluic acid glucuronides in animals. Xylene causes mucus irritation and affects the central nervous system (CNS) in humans and animals after acute inhalation exposure. Hepatic effects have been noted in humans after acute inhalation exposure to high concentrations and in rats after subchronic oral or inhalation exposure. No consistent developmental or reproductive effects were observed in the studies found in the available literature. Commercial xylene and all three isomers have generally tested negative for genotoxicity. Xylenes are currently not classifiable as to carcinogenicity by the International Agency for Research on Cancer (IARC) or the Environmental Protection Agency (EPA).

The AEGL-1 is based on the no-effect level for notable discomfort in human subjects. Only mild eye irritation was noted during a 30-min exposure to mixed xylenes at 400 ppm (Hastings et al. 1984). An interspecies uncertainty factor was not applied because the key study used human data. An intraspecies uncertainty factor of 3 was applied because slight eye irritation is caused by a

direct effect of the chemical and the response is not expected to vary greatly among individuals. Because irritation is considered a threshold effect, which should not vary over time, the AEGL-1 value was not scaled across time, but rather the same value is applied at all times. The resulting value of 130 ppm is supported by several other studies, including a 150-ppm *p*-xylene exposure resulting in eye irritation in a contact lens wearer (Hake et al. 1981); a 15-min exposure to mixed xylenes at 230 ppm resulting in mild eye irritation and dizziness with no loss of coordination in one individual (Carpenter et al. 1975b); and a 3-h exposure to *m*- or *p*-xylene at 200 ppm (Ogata et al. 1970), a 4-h exposure to *m*-xylene at 200 ppm (Savolainen et al. 1981), and a 5.5-h exposure to *m*-xylene at 200 ppm (Laine et al. 1993), all representing no-effect levels for notable discomfort.

The AEGL-2 is based on the no-effect level for impaired ability to escape. During a 4-h exposure to mixed xylenes at 1,300 ppm, rats developed poor coordination (slight coordination loss) after 2 h of exposure, returning to normal coordination postexposure (Carpenter et al. 1975b). The point of departure of 1,300 ppm for 2 h therefore represents the threshold for reversible equilibrium disturbances and the no-effect level for impaired ability to escape. This concentration and end point are consistent with the preponderance of available data for 4-h exposures in rats: the median effective concentration (EC_{50}) for decreased rotarod performance was 1,982 ppm (Korsak et al. 1993); the minimum narcotic concentration for *m*-, *o*-, and *p*-xylene ranged from 1,940 to 2,180 ppm (Molnár et al. 1986); and exposure to *p*-xylene at 1,600 ppm resulted in hyperactivity, fine tremor, and unsteadiness (Bushnell 1989) and caused changes in the flash evoked potential suggestive of increased arousal (Dyer et al. 1988). It is assumed that the CNS response observed after xylene exposure is directly related to the concentration of parent material reaching the brain, and that venous blood concentrations (CV) correlate with brain concentrations. Therefore, the CV of xylene after a 2-h exposure to xylene at 1,300 ppm is expected to provide an internal dose measurement correlating with the clinical sign of poor coordination. With a physiologically based pharmacokinetic (PBPK) model (see Appendix C), the internal dose (CV) producing impaired coordination in rats was determined. Then, the human PBPK model was run for each defined AEGL time period to determine the equivalent exposure concentration producing the target CV.

The AEGL-3 derivation is based on reversible prostration in rats and a no-observed-effect level (NOEL) for death in rats exposed to 2,800 ppm for 4 h (Carpenter et al. 1975b). Although coordination initially remained poor, it returned to normal the next day. This concentration represents a threshold for marked CNS depression, which could lead to death. As for the AEGL-2, it is assumed that the CNS effects observed after xylene exposure are directly related to the concentration of parent material reaching the brain. Therefore, PBPK modeling (see Appendix C) was again used to calculate the internal dose (CV) correlating with an exposure of rats to 2,800 ppm for 4 h that produced prostra-

tion. The human PBPK model was then run for each defined AEGL time period to determine the equivalent exposure concentration producing the target CV.

A total uncertainty factor of 3 was applied to the AEGL-2 and -3 dose metrics. An intraspecies uncertainty factor of 3 was applied for the pharmacokinetic and pharmacodynamic uncertainty because the minimum alveolar concentration (MAC) for volatile anesthetics should not vary by more than 2- to 3-fold among humans (NRC 2002). An interspecies uncertainty factor of 3 would usually be applied. PBPK modeling reduced the toxicokinetic component of the uncertainty factor to 1, but the pharmacodynamic component would normally be retained and assigned a 3 (although it appears that similar CNS effects occur in humans and animals, it is not known if they occur at the same tissue dose). A total uncertainty factor of 10, however, drives the 8-h AEGL-2 value to 180 ppm and the 4-h AEGL-3 value to 447 ppm. These amounts are exposure concentrations that humans are known to tolerate with minimal or no adverse effects. With regard to the AEGL-2, humans exposed to *p*-xylene at 150 ppm for 7.5 h exhibited no effects on performance tests and noted only mild eye irritation (Hake et al. 1981). With regard to the AEGL-3, numerous human studies investigated the effects of exposure to *m*-xylene at 130 to 200 ppm for 4 to 6 h, with 20-min peaks of 400 ppm with or without exercise, and found no effect or reported minimal CNS effects (Savolainen and Linnavuo 1979; Savolainen et al. 1984, 1985a,b; Seppalainen et al. 1989, 1991; Laine et al. 1993). Therefore, the interspecies uncertainty factor is reduced to 1, and a total uncertainty factor of 3 is applied to the AEGL-2 and AEGL-3 values (NRC 2002).

The proposed xylene AEGL values apply to all three xylene isomers or a mixture of xylene isomers. No significant differences in the potency of the isomers after oral or inhalation exposure were identified, metabolism of each isomer proceeds via the same pathways, and PBPK model predictions indicate that the internal dose (CV) after exposure does not vary significantly among the individual isomers.

The AEGL values are listed in Table 6-1. AEGL-2 and AEGL-3 values are greater than 10% of the lower explosive limit.

1. INTRODUCTION

Commercial or mixed xylene is composed of three isomers: *meta*-xylene (*m*-xylene), *ortho*-xylene (*o*-xylene), and *para*-xylene (*p*-xylene), of which the *m*-isomer usually predominates (40% to 70% of the mixture) (Fishbein 1988; ATSDR 2007). The exact composition of the isomers depends on the xylene formulation. Ethylbenzene is often present in mixed xylenes; in fact, the technical product contains approximately 40% *m*-xylene and approximately 20% each *o*- and *p*-xylene and ethylbenzene (Fishbein 1988). Other minor contaminants of xylene include toluene and C_9 aromatic fractions. Mixed xylenes are used in production of the individual isomers or ethylbenzene, as a solvent, in paints and coatings, and as a blend in gasoline (Fishbein 1988; ATSDR 2007). The annual

production capacity of mixed xylenes has been estimated at 13.1 billion pounds, with 1990 and 1991 production estimates of about 6 billion pounds (ATSDR 2007). The individual isomers are used primarily as chemical intermediates (OECD 2003). Almost all *o*-xylene produced in the United States is consumed in the manufacture of phthalic anhydride. Other minor uses include the use of *o*-xylene as a feedstock in the production of bactericides, soybean herbicides, and dyes. Most *m*-xylene is used as a chemical intermediate in the production of isophthalic acid. Small amounts of *m*-xylene are also consumed in the production of *m*-tolic acid, isophthalonitrile, and other compounds. Almost all U.S. production of *p*-xylene is consumed in the manufacture of dimethyl terephthalate and terephthalic acid, which are used in the production of polyester fiber and plastics.

The physical and chemical properties of xylenes are presented in Table 6-2. The odor of xylenes is described as an aromatic hydrocarbon odor. The odor threshold ranges between 0.8 and 40 ppm, and the irritating concentration is 100 ppm (Ruth 1986).

TABLE 6-1 Summary of Proposed AEGL Values for Xylenes

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (Nondisabling)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	Eye irritation in human volunteers exposed to mixed xylenes at 400 ppm for 30 min (Hastings et al. 1984)
AEGL-2 (Disabling)	2,500 ppm[a] (11,000 mg/m^3)	1,300 ppm[a] (5,600 mg/m^3)	920 ppm[a] (4,000 mg/m^3)	500 ppm (2,200 mg/m^3)	400 ppm (1,700 mg/m^3)	Rats exposed to mixed xylenes at 1,300 ppm exhibited poor coordination 2 h into a 4-h exposure (Carpenter et al. 1975b)
AEGL-3 (Lethal)	—[b]	3,600 ppm[a] (16,000 mg/m^3)	2,500 ppm[a] (11,000 mg/m^3)	1,300 ppm[a] (5,600 mg/m^3)	1,000 ppm[a] (4,300 mg/m^3)	Rats exposed to mixed xylenes at 2,800 ppm for 4 h exhibited prostration followed by a full recovery (Carpenter et al. 1975b)

[a]Concentrations are at or higher than 1/10th of the lower explosive limit (LEL) for all forms of xylene (*o*-xylene LEL, 9,000 ppm; *m*- and *p*-xylene LEL, 11,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.
[b]10-min AEGL-3 = 7,200 ppm is ≥50% of LEL. Therefore, extreme safety considerations against the hazards of explosions must be taken into account.

TABLE 6-2 Physical and Chemical Data for Xylenes

Parameter	Value	Reference
Synonyms	Dimethylbenzene (1,2-; 1,3-; or 1,4-); xylol, *m*-xylene (*m*-isomer); *o*-xylene (*o*-isomer); *p*-xylene (*p*-isomer); methyltoluene	ACGIH 1991; Budavari et al. 1996
CAS registry no.	1330-20-7 108-38-3 (*m*-isomer) 95-47-6 (*o*-isomer) 106-42-3 (*p*-isomer)	
Chemical formula	C_8H_{10}	Budavari et al. 1996
Molecular weight	106.17	Budavari et al. 1996
Physical state	Liquid	Budavari et al. 1996
Color	Colorless	Budavari et al. 1996
Melting point	No data for mixture −47.4°C (*m*-isomer) −25°C (*o*-isomer) 13-14°C (*p*-isomer)	Budavari et al. 1996
Boiling point	137-140°C	Budavari et al. 1996
Solubility	Practically insoluble in water; 106 mg/L at 25°C	ATSDR 2007
Vapor pressure at 21°C	6.72 mmHg	ATSDR 2007
Density	0.864 g/cm^3	ATSDR 2007
Log K_{OW}	3.12-3.20	ATSDR 2007
Conversion factors in air	1 ppm = 4.34 mg/m^3 1 mg/m^3 = 0.23 ppm	NRC 1984

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Three men were employed to paint a double-bottomed tank in the engine room of a ship (Morley et al. 1970). Solvent composed 34% of the total weight of the paint, with xylene composing in excess of 90% of the solvents, and only a trace amount of toluene was present. The men started work at 10:30 am, and after being reported missing later that evening were found unconscious at 5:00 am the next day. The first patient was dead upon admission to the hospital. Autopsy revealed severe pulmonary congestion with focal alveolar hemorrhage and acute pulmonary edema, hepatic congestion with swelling and vacuolization of many cells in the centrilobular areas, and microscopic petechial hemorrhages in

both the gray and white matter of the brain. In addition, evidence of axonal neuronal damage was indicated by swelling and loss of Nissl substance. The second patient was admitted to the hospital unconscious, exhibiting only a slight response to painful stimuli. He was also hypothermic, had a flushed face, and had peripheral cyanosis. Medium-grade moist sounds were present in his lungs, and a chest x-ray revealed patchy diffuse opacity in both lungs. Five hours after treatment with tracheal aspiration and oxygen, the patient regained consciousness, but was amnesic for 2 to 3 days. Evidence of renal damage was indicated by an increase in blood urea of 59 mg/100 milliliters (mL) to 204 mg/100 mL 3 days after admission. Endogenous creatinine clearance was also reduced at this time. Slight hepatic impairment was indicated by a rise in serum transaminase activity to 100 international units (IU) over 48 h, followed by a return to normal levels. Patient 3 recovered consciousness after admission and was confused and amnesic, had slurred speech, and was ataxic upon walking. Within 24 h of admission, he was fully conscious and alert, and the ataxia disappeared over 48 h. There was no evidence of renal impairment, and slight hepatic impairment was indicated by a slight rise in serum transaminase activity (52 IU) over 48 h, followed by a return to normal levels.

The circumstances of the accident were re-created by the study authors. On the basis of the quantity of paint applied, the volume of the space, and the assumption of still air conditions (based on the limited ventilation present), the probable xylene concentration was estimated to have been 10,000 ppm. Although two cans of cleaning fluid composed primarily of toluene were also found at the scene, neither of the survivors remembered using the cleaning fluid. Therefore, it was assumed by the study authors that exposure was mainly to xylene.

2.2. Nonlethal Toxicity

2.2.1. Case Reports

Two case reports of seizures after exposure to xylene-based products have been reported in the literature. Goldie (1960) reported a case in which eight painters were exposed to paint containing 80% xylene and 20% methylglycolacetate. When they were painting the inside of a gun tower, adequate ventilation was not present because the ventilation system created too great a draft for painting. The workers complained of headache, vertigo, gastric discomfort, dryness of the throat, and slight drunkenness after 30 min of exposure; therefore, the painters worked in the unventilated area for 30 min at a time followed by 10-min breaks to breathe fresh air. After working for about 2 months, an 18-year-old male exhibited behavior indicative of a convulsive seizure one day after leaving work. Signs included weakness, dizziness, inability to speak, unconsciousness, eyes and head rotated to one side, chewing but no foaming, and short, sharp interrupted jerks of the upper and lower limbs. The patient recov-

ered consciousness 20 min later. Although the patient experienced another shorter seizure after admission to the hospital, hospital tests were unable to confirm the diagnosis. In another case, Arthur and Curnock (1982) reported that an adolescent male developed major and minor seizures after using a xylene-based glue used for building model airplanes. Neither case report provides an exposure concentration, and exposures were not limited to xylene.

Klaucke et al. (1982) reported that during work one day, 15 male and female employees of a small community hospital reported at least two of the following symptoms lasting from 2 to 48 h: headache, nausea, vomiting, dizziness or vertigo, eye irritation, and nose or throat irritation. The frequency of the symptoms was as follows: headache, 12/15; nausea, 10/15; eye irritation, 8/15; nose or throat irritation, 7/15; dizziness or vertigo, 7/15; and vomiting, 6/15. Fourteen of the 15 employees noted an unusual odor 15 to 30 min before the onset of symptoms. After investigation, it was determined that the "illness" was caused when 1 L of liquid xylene was poured down a drain in a pathology laboratory, and the vapors were then drawn into the room, which contained a ventilation fan that distributed the vapors throughout the affected area of the hospital. It was estimated that workers were exposed to levels as high as 700 ppm.

2.2.2. Controlled Exposures

Twenty-three male volunteers (mean age 23 years) were divided in groups of four or five and exposed to air containing measured concentrations of *m*-xylene, *p*-xylene, or toluene at 100 or 200 ppm for 3 h or for 7 h with a 1-h lunch break (Ogata et al. 1970). Vapor concentrations were analyzed every half-hour by gas chromatography. Systolic and diastolic blood pressure, pulse rate, flicker value, and reaction time were assessed in all volunteers at the beginning and end of exposures. Exposure to *m*- or *p*-xylene did not significantly influence any of these parameters.

Six or seven7 volunteers (21 to 60 years of age; sex not provided) were exposed to air containing measured concentrations of mixed xylenes (*p*-xylene, 7.84%; *m*-xylene, 65.01%; *o*-xylene, 7.63%; ethylbenzene, 19.27%) for 15 min in the following order: 230, 110, 460, or 690 ppm, with exposures limited to one per day (Carpenter et al. 1975a,b). Volunteers provided written responses at 1-min intervals throughout the 15-min exposure. Xylene concentration was analyzed by gas chromatography. Results of the exposure are summarized in Table 6-3. Complaints at 110 ppm were limited to mild throat discomfort in one volunteer during the first and seventh minute of exposure; this individual did not experience discomfort during exposure to 230 ppm. Exposure to 230 ppm resulted in one volunteer complaining of eye irritation during the 4th, 5th, and 15th minute of exposure; another noting sleepiness at the 13th minute followed by eye wetness (but no tears formed) at the 14th and 15th minute of exposure; one volunteer reporting possible mild nasal irritation; and another volunteer reporting

TABLE 6-3 Xylene Irritation Thresholds (Subjects Exposed for 15 Min)

Condition of Subjects	Concentrations (ppm)			
	110	230	460	690
Volunteers	6	7	6	6
Throat irritation	1	0	1	2
Eye irritation	0	1	4	4
Tears	0	1	1	2
Dizziness and light-headedness	0	1	1	4

Source: Carpenter et al. 1975b. Reprinted with permission; copyright 1975, *Toxicology and Applied Pharmacology*.

intermittent dizziness and light-headedness (with no loss of coordination) during the last 2 min of exposure. At 460 ppm, four volunteers reported intermittent or continuous mild eye irritation, with one additionally reporting eye wetness when leaving the chamber; one volunteer noted mild dizziness at the sixth minute of exposure that persisted throughout the 15-min exposure (the same individual who noted dizziness at 230 ppm); and one volunteer reported possible mild nasal and throat irritation (the same individual who reported nasal irritation at 230 ppm). Exposure to 690 ppm resulted in dizziness and light-headedness in four volunteers. Three of the volunteers reported the dizziness to be mild and not associated with a loss of balance, while the other volunteer reported a slight loss of balance. Eye, nose, and throat irritation was noted during exposure but ceased within 10 min postexposure. Carpenter and associates (1975b) concluded that exposure to xylene at 100 ppm would not be objectionable to most people, while none of the volunteers thought that 690 ppm could be tolerated over an 8-h work day.

Volunteer male college students 18 to 30 years old were exposed to air containing mixed xylenes at 0, 100, 200, or 400 ppm (0, 0.43, 0.86, and 1.72 mg/L) for 30 min (*p*-xylene, 7.84%; *m*-xylene, 65.01%; *o*-xylene, 7.63%; ethylbenzene, 19.27%) (Hastings et al. 1984). The students were exposed using an olfactometer delivery hood made of transparent Lucite, which allowed adequate air flow. Solvent or distilled water (for control exposures) was delivered with a motorized syringe, and heating tapes vaporized the solvent or water before introduction into the hood. Samples of air taken from the breathing zone in the hood were analyzed by gas chromatography for the actual exposure concentrations and were acceptable. A contact electrode was taped near the skin of the outer canthus of one eye on each subject to measure eye blinks, and an indifferent electrode was clipped to the ipsilateral ear. Respiratory measurements were recorded with the aid of a thermistor placed near one naris. Behavioral tests, two measuring psychomotor performance (consisting of the Michigan Eye-Hand Coordination Test and a visuomotor-skill TV game) and one measuring cognitive performance (choice reaction time), were administered before, during, and

after exposure (10 min after placement in the hood when exposed to control air, during the last 5 min of the 30-min exposure to xylene, and 10 min after the subjects were again exposed to control air for 10 min). The reader is referred to the study for additional details about the behavioral testing. The subjects were asked every 5 min during the experiment if they detected any odor or experienced eye, nose, or throat irritation.

The only clear concentration-related effect of exposure in the Hastings et al. (1984) study was mild eye irritation reported by 56%, 60%, 70%, and 90% of the subjects in the 0-, 100-, 200-, and 400-ppm groups, respectively (not statistically significant). No concentration-related increase in the percentage of exposed subjects experiencing nose or throat irritation was observed and the number of eye blinks per minute and respiration rate (breaths per minute) were not statistically increased in any of the exposure groups compared with the controls, confirming that the reported irritation was mild. No statistically significant differences in the performance of the behavioral tasks by the exposed subjects were observed compared with controls.

Gamberale et al. (1978) conducted two series of experiments assessing the effects of xylene exposure in healthy male volunteers age 21 to 33 years. In the first investigation, groups of five males were exposed to xylene at 0, 100, or 300 ppm for 70 min on day 1, 2, or 3, with the sequence of the exposure balanced among the three groups (on day 1, groups 1, 2, and 3 were exposed to 0, 300, and 100 ppm, respectively). In the second investigation, a group of eight volunteers (who had also participated in the first series) were exposed to xylene at 300 ppm for 70 min; they exercised four times per day on a bicycle equipped with an ergometer at 100 watts [W]) for the first 30 min of exposure and sat in a chair the remaining 40 min of exposure. In both experiments, a breathing valve with low resistance was used to supply the air or xylene, and menthol crystals were placed in the tube of the mouthpiece to mask the odor of solvent. A total hydrocarbon analyzer was used to continuously measure the inspired xylene concentration during exposure, and a gas chromatographic technique was used to measure the alveolar air concentration of xylene (further details were not provided). Heart rate was checked regularly. Five performance tests were administered to volunteers during the exposures: one administered at the beginning of the exposure period and all five during the last 35 min of exposure. The performance tests included critical flicker fusion, reaction time addition, simple reaction time, short-term memory, and choice reaction time. All the tests utilized visual stimulation with electronic recording of responses. After each exposure trial, subjects were asked to fill out a questionnaire addressing subjective symptoms experienced during exposures.

The concentration of xylene in the alveolar air at 30 and 70 min of exposure corresponded to the nominal concentration: the alveolar air concentration in the 300-ppm group was three times that of the 100-ppm group (Gamberale et al. 1978). After subjects exercised during exposure to 300 ppm, the alveolar xylene concentration increased 3.7- and 2.2-fold at 30 and 70 min, respectively, compared with exposure to 300 ppm at rest. No exposure-related changes in heart

rate were observed. Although a slight increase in the frequency of headache and feeling of "sickness" were noted, the number of subjects with these complaints was not provided. However, the authors stated that most subjects reported no or negligible symptoms. Xylene exposure at rest did not significantly affect the results of the performance tests of subjects exposed to xylene at 100 or 300 ppm. When xylene exposure was combined with 100 W of work, impaired performance was observed on all tests, significantly so ($p < 0.05$) in the reaction time addition test and the short-term memory test (further details not provided).

Exposure of groups of four male volunteers to *p*-xylene at 70 ppm, toluene at 80 ppm, or a combination of toluene at 50 ppm and *p*-xylene at 20 ppm for 4 h did not affect the results of choice reaction time, simple reaction time, or short-term memory performance tests as assessed by microcomputers immediately upon entry into the exposure chamber, after 2 h of exposure, or after 4 h of exposure compared with control air exposure (Olson et al. 1985). Solvent exposure did not affect heart rate or the reporting of subjective symptoms recorded by questionnaire at the end of the exposures.

Groups of two healthy male volunteers aged 22 to 35 years were exposed in random sequence to air containing toluene at 100 ppm, xylene at 100 ppm, a mixture of toluene at 50 ppm and xylene at 50 ppm, or control air for 4-h sessions, with each exposure session separated by 7-day intervals (Dudek et al. 1990). No information about the purity or composition of xylene was provided. Exposures occurred in a chamber, with the test solvent concentrations controlled by monitoring with gas chromatography and infrared spectrophotometry. Terpon vapors were used to mask the odor of the test solvents. A battery of nine psychological tests was used to evaluate the effects of the solvents on the subjects during exposure. The tests evaluated memory (Sperling's test), interference of cognitive processes (Stroop's test), cognitive processes (Sternberg's test), motor-visual coordination (Flanagan's test), speed and precision of hand movements (aiming), psychomotor efficiency (simple reaction time, choice reaction time, and Santa Ana), and mood (profile of mood state). The volunteers completed a training session on these performance tests 1 week before the exposure. On the day of the exposure, the performance tests were administered 1 h before exposure, at the commencement of exposure, and 3 h into the exposure; only the results with xylene are reported here. Xylene exposure for 3 h resulted in significant reductions in performance of the simple reaction time test (prolongation of simple reaction time; $p < 0.001$) and the choice reaction time test ($p < 0.001$). No statistically significant effects were observed in any of the other psychological tests.

An average of 10 subjects (mix of males and females) were exposed to xylene in a 1,200-cubic-foot gas chamber for 3 to 5 min, and the level of irritation experienced by the subjects was recorded upon exit from the chamber (Nelson et al. 1943). Further experimental details were not provided. The study authors reported that exposure to xylene at 200 ppm resulted in eye, nose, and throat irritation in most subjects and it was classified as objectionable.

In 1981, Hake et al. published the results of a study that established the relationship between exposure concentration and *p*-xylene body burden as measured by urine, blood, breath, and saliva, and they evaluated the effects of repeated *p*-xylene vapor exposure in humans. Nine adult Caucasian males and seven adult Caucasian females were exposed at rest to *p*-xylene vapors. The subjects were subdivided into three daily groups for 7.5, 3, or 1 h of daily exposures. Males and females were exposed the first week (five consecutive days) to *p*-xylene at 100 ppm. Males were also exposed to 20 ppm the second week, 150 ppm the third week, and fluctuating concentrations of 50 to 150 ppm (for a time-weighted average [TWA] of 100 ppm) the fourth week. Subjects were exposed to 0 ppm Thursday and Friday of the week preceding xylene exposure, and Monday and Tuesday of the week following the last week of xylene exposure to provide control data. Exposures were conducted in a controlled environment chamber (20 × 20 × 8 feet). The *p*-xylene vapor was introduced into the chamber's circulating air by a stream of air-sweeping vapor from a warm flask. The *p*-xylene chamber vapor concentrations were continuously monitored and an infrared spectrometer with a gas chromatograph served as a back-up monitor. End points selected to evaluate *p*-xylene included neurologic testing (modified Romberg, heel-to-toe test, electroencephalogram [EEG], and visual evoked potentials [VEPs]), cardiopulmonary function tests, cognitive testing (Flanagan coordination test, time estimation tests, arithmetic test, inspection test), and subjective responses (noted by these volunteers during the exposure or during the first 3 h of exposure).

Irritation was the only subjective response noted that was related to xylene exposure (Hake et al. 1981). In males, eye irritation was noted seven times and eight times during the week-long exposures to 100 and 150 ppm, respectively, compared with three mentions during the four control days. Of these notations, one individual in the 7.5-h exposure group wearing contact lenses noted eye irritation almost every day, while another subject complained twice at 100 ppm and three times at 150 ppm. No irritation was noted by males during any 3-h exposure, but one subject complained of eye irritation during a 1-h exposure to 150 ppm. No visible reddening of the eyes or conjunctiva was observed. Irritation was also noted by females, but it was confined to nose and throat irritation. During the 5-day exposure to 100 ppm, irritation was noted 17 times, compared with 5 times during two control days. No significant neurologic, cardiopulmonary, or cognitive abnormalities were definitively correlated with exposure to any concentration of *p*-xylene. Although a decrement in the performance of the Flanagen coordination test was noted in males exposed to *p*-xylene at 150 ppm for 7.5 h/day, the decrement was almost entirely due to the performance of one subject who had previously been ill. The changes in EEG activity (increase in delta activity) observed in males exposed for 7.5 h to *p*-xylene at 100 or 150 ppm could not definitely be ascribed to exposure because the changes were not evident during every exposure and were not correlated with exposure concentration.

Nine male student volunteers (aged 20 to 25 years) were exposed at rest to *m*-xylene at 200 ppm, trichloroethane at 200 or 400 ppm, or a combination of xylene at 200 ppm and trichloroethane at 400 ppm for 4 h/day, once a week, with a 6-day interval between succeeding exposures over six consecutive weeks (Savolainen et al. 1981; Seppalainen et al. 1983). The exposures were single blind, with each subject acting as his own control. The end points examined by each author were body sway, reaction times, flicker fusion, and subjective symptoms (Savolainen et al. 1981) and pattern VEP (Seppalainen et al. 1983). Body sway along the anteroposterior and lateral axes was recorded with a strain gauge platform with the eyes open and closed and was measured 1 h before exposure and after 20 min and 3.75 h of exposure. Reaction time (manual response to stimuli) and tapping of the dominant hand was measured before exposure, and after 1 and 3 h of exposure. Flicker fusion was assessed before exposure and at 1.5 and 3.5 h of exposure. Pattern VEP was measured before exposure and 5 to 30 min after exposure ended. Exposure to xylene alone did not result in any marked adverse effects. A slight improvement in performance was observed as a slight decrease in body sway and slightly shortened reaction time (Savolainen et al. 1981). No effects on tapping speed were observed, and a slight increase in the critical fusion thresholds were noted in the afternoon sessions (Savolainen et al. 1981). No statistically significant effects were observed in the pattern VEP after exposure to *m*-xylene (Seppalainen et al. 1983).

Nine male student volunteers (mean age 21 years) in three groups of three, were exposed for 3 h in the morning and 40 min in the afternoon, with a 40-min lunch break, to air containing a fixed concentration of *m*-xylene at 200 ppm, a basal concentration of *m*-xylene at 135 ppm with 20-min peak concentrations of 400 ppm at the beginning of the morning and afternoon sessions, or to control air (Seppalainen et al. 1989, 1991; Laine et al. 1993). The subjects were exposed sedentary or with 10 min of exercise (100 W) at the beginning of each exposure session. The exposures occurred on six separate days, with a minimum of a 5-day interval separating the xylene exposures. The subjects were exposed in a dynamic chamber, and the concentration of atmospheric xylene was continuously monitored (further details not provided). Peppermint oil was used to mask control exposure and the solvent odor, with the experiment being a single-blind experiment with crossover design, with each subject acting as his own control. The end points examined by each author were VEPs and brainstem auditory evoked potentials (BAEPs) (Seppalainen et al. 1989), EEG recordings (Seppalainen et al. 1991), and body sway and reaction times (Laine et al. 1993).

VEPs were recorded in the morning before the subjects entered the exposure chamber and at the end of the morning and afternoon exposure session (Seppalainen et al. 1989). For pattern VEPs (pattern reverse stimulus), latencies of P50, N70, P100, N135, P170, and the peak-to-peak amplitude of N70 to P100 were measured. For flash VEPs (light flash), latencies of P50, N70, P100, N150, P200, and the peak-to-peak amplitude of P100 to N150 were measured. BAEPs were also recorded. The results from the study demonstrated that xylene exposure at rest did not result in any consistent effects on VEPs, while xylene expo-

sure combined with exercise resulted in minor but statistically significant decreases in the latency of N135 in the pattern VEP and of P200 in the flash VEP at fluctuating concentrations of 400 ppm. No exposure-related changes were noted in BAEPs. The study authors suggested that "the most intensive exposure situations" may result in an aroused state but that the changes did not indicate hazards to healthy workers.

EEG recordings were made during the first 18 min of the morning and afternoon exposure sessions and included 10 min of exercise and 3 to 4 min after exercise ceased on the days subjects were exercising (Seppalainen et al. 1991). Five-minute recordings were also made 1 and 2 h after the subject entered the chamber in the morning and 45 min after the afternoon exposure ceased. Exposure to *m*-xylene resulted in minor changes that suggested a stimulating, excitatory effect (slight alpha activation).

Body sway and reaction times were measured before exposure in the morning, 20 and 120 min after the beginning of the morning exposure, 20 min after the beginning of the afternoon exposure, and 50 min after termination of the afternoon exposure (Laine et al. 1993). Body sway along the anteroposterior and lateral axes was recorded with a strain gauge platform with the eyes open and closed. Simple reaction time of the dominant hand after visual stimuli and choice reaction time after auditory and visual stimuli were used to assess reaction times. The authors also measured gaze deviation nystagmus. Exposure to peak concentrations of *m*-xylene (400 ppm) resulted in decreased body sway in sedentary and exercising subjects. No definitive conclusions on the effects of *m*-xylene exposure on reaction times could be drawn because reaction times did not consistently change with the intensity of exposure. In the afternoon, longer simple reaction times were noted after exposure to peaks of *m*-xylene at rest, while prolonged audiomotor choice reaction times were prolonged after exposure to peaks of *m*-xylene while exercising. No nystagmus was noted.

Laine et al. (1993) also exposed 12 healthy male volunteers (four groups of three) at rest to stable concentrations of *m*-xylene at 200 ppm for 5 h and 30 min on 2 days, with 1 week separating the exposures. Body sway and reaction time (auditory, visual, and associative signals) were measured in the morning before exposure and after cessation of the exposure. Body movement while the subjects slept was recorded the night of the exposure at each subject's home using a static charge sensitive bed. No effect on body sway was observed, and no statistical difference in reaction times was noted. The only statistically significant effect observed when the subjects were sleeping was a slightly decreased number of body movements. No effect on active and quiet sleep was observed. No differences in body sway or reaction time were observed the morning after the exposure.

Nine male student volunteers (mean age 21 years) in three groups of three were exposed for 3 h in the morning and 1 h in the afternoon, with a 40-min lunch break, to air containing a fixed concentration of *m*-xylene at 200 ppm, a basal concentration of *m*-xylene at 135 ppm with 20-min peak concentrations of 400 ppm at the beginning of the morning and afternoon sessions, or to control

air (Savolainen et al. 1984, 1985a,b). The subjects were exposed sedentary or with 10 min of exercise (100 W) at the beginning of each exposure session. The exposure occurred at 6-day intervals during six succeeding weeks. The subjects were exposed in a dynamic chamber, and the concentration of atmospheric xylene was continuously monitored with an infrared monitor. Peppermint oil was used to mask control exposure and the solvent odor, with the experiment being a single-blind experiment with crossover design, with each subject acting as his own control. The end points examined by each author were body sway (Savolainen et al. 1985a) and body sway and reaction time (Savolainen et al. 1984, 1985b). Body sway along the anteroposterior and lateral axes was recorded with a strain gauge platform with the eyes open and closed and was measured before exposure in the morning, at the time of peak exposure and exercise (about 15 to 20 min into exposure), and after exposure. Simple reaction time of the dominant hand following visual stimuli and choice reaction time following auditory stimuli or auditory and visual stimuli were used to assess reaction times (Savolainen et al. 1984, 1985b).

Savolainen et al. (1984) found that body sway along the anteroposterior axis was impaired by exposure to peak xylene concentrations at rest but improved with peak xylene concentrations with exercise. Opposite results were observed when body sway was measured along the lateral axis: only fluctuating concentration with exercise impaired balance, while body sway improved (decreased) with exposure at rest. Savolainen et al. (1985b) found that body sway was negatively correlated with xylene concentration; that is, xylene exposure improved (decreased) body sway, while no correlation was evident between blood xylene concentration and body sway. In contrast, Savolainen et al. (1985a) reported that changes in body sway were positively correlated with blood xylene concentration from exposure to stable and fluctuating *m*-xylene concentrations.

No consistent, significant effects on reaction time after exposure to *m*-xylene were found by Savolainen et al. (1985b). Savolainen et al. (1984) reported that choice reaction times as assessed by using auditory stimuli were statistically impaired in subjects exposed to peak *m*-xylene concentrations with exercise during the afternoon session. In the afternoon sessions, simple reaction times were impaired in sedentary subjects after peak exposure to *m*-xylene but improved in subjects exposed to peak concentration with exercise.

A total of 22 male student volunteers (mean age 24 years) were exposed to laboratory grade *m*-xylene (Riihimaki and Savolainen 1980; Savolainen and Riihimaki 1981). Six sedentary subjects were exposed for 6 h/day (with a 1-h lunch break) for five consecutive days and for 1 to 3 days after a 2-day weekend. Exposures on Monday to Friday were to stable concentrations of 100 ppm for the morning and afternoon sessions except on Friday afternoon when the concentration was doubled to 200 ppm. Exposures on Monday to Wednesday of the following week were to fluctuating concentrations of *m*-xylene: subjects were exposed to an approximate baseline concentration of 70 ppm with peaks of 200 ppm lasting 10 min (TWA of 100 ppm). On Wednesday afternoon, exposure concentrations were approximately doubled (baseline concentration of 130 ppm

with peaks of 400 ppm; TWA of 200 ppm). The remaining 16 subjects were divided into two groups of eight. Both groups exercised on a bicycle ergometer at 100 W 4×/day for 10 min, exercising at 1 and 2 h of exposure in the morning and afternoon sessions. One group was exposed to a stable concentration of *m*-xylene at 100 ppm, with concentrations doubled to 200 ppm Friday afternoon, and the other group was exposed to fluctuating concentrations (baseline concentration of 70 ppm with hourly peaks of 200 ppm over 10 min; mean concentration of 100 ppm), with concentrations doubled on the last day (baseline concentration of 130 ppm with peaks of 400 ppm; mean concentration of 200 ppm). The subjects were exposed in a dynamic chamber, with peppermint oil used to mask control exposure and the solvent odor. Control days preceded and succeeded exposure days, so that each subject acted as his own control. The end points examined by each author included body sway (Riihimaki and Savolainen 1980; Savolainen and Riihimaki 1981), subjective symptoms, choice and simple reaction times, critical flicker fusion, Santa Ana manual dexterity test, nystagmus, and EEG recordings on a limited number of subjects (Riihimaki and Savolainen 1980).

Body balance was affected when a rapid increase in blood xylene concentration occurred (after peak exposures to fluctuating concentrations, particularly to 400 ppm), with tolerance developing upon continuing exposure (Riihimaki and Savolainen 1980; Savolainen and Riihimaki 1981). Changes in EEG recordings suggestive of a slight decrease in vigilance (increased number of slow occipital transients) were observed in 4/4 subjects after exposure to peak concentrations of xylene combined with exercise (Riihimaki and Savolainen 1980). One volunteer also exhibited bilateral spike and wave complexes. Although Riihimaki and Savolainen (1980) reported impairment of simple and choice reaction times after exposure to xylene with the development of tolerance upon continuing exposure, further details were not provided. Xylene exposure did not affect nystagmus, Santa Ana manual dexterity test, or critical flicker fusion (Riihimaki and Savolainen 1980). Symptoms were limited to mild nose and throat irritation reported by 1/6 sedentary subjects during the 400-ppm peaks (Riihimaki and Savolainen 1980). The results of testing the 6 sedentary subjects and the 16 volunteers divided into 2 groups of 8 were also reported by Savolainen et al. (1979b) and Savolainen et al. (1980), respectively.

Savolainen and Linnavuo (1979) assessed body balance in 17 healthy male volunteers (mean age 24 years) by means of a strain gauge transducer. Then, 6 of the 17 volunteers were exposed to *m*-xylene in the morning for 3 h to a TWA of 100 ppm with hourly peaks of 200 ppm and in the afternoon for 3 h to a TWA of 200 ppm with hourly peaks of 400 ppm, with a 1-h lunch break separating the morning and afternoon exposures. Body balance was assessed 1 h before the morning exposure and at the end of the morning and afternoon sessions. Control days preceded and succeeded exposure days. Although no differences in body balance were observed after xylene exposure in the morning session, impaired body balance was noted in the subjects during the afternoon session, particularly with the eyes closed.

With six xylene concentrations (composition not specified) and 18 subjects familiar with the smell of xylene, the odor threshold for xylene was reported as 0.1 to 0.4 ppm (reported as 0.6 to 1.9 mg/m^3) for the minimum perceptible concentration and 0.09 to 0.3 ppm (0.4 to 1.4 mg/m^3) for the maximum imperceptible concentration (Gusev 1965). EEG recordings of four subjects exposed to xylene for 6 min indicated reductions in the electrical activity of the cerebral cortex at 0.07 ppm (0.32 mg/m^3) but not at 0.05 ppm (0.21 mg/m^3). The reason for this effect at this relatively low exposure concentration is unknown.

2.3. Developmental and Reproductive Effects

A limited number of studies suggest an association between xylene exposure and an increased risk of spontaneous abortion (Windham et al. 1991; Taskinen et al. 1994) or developmental toxicity (Kucera 1968; Holmberg and Nurminen 1980; Taskinen et al. 1989). A number of limitations preclude the usefulness of these studies, including small sample sizes, no quantified exposure concentrations, and concurrent exposures to other solvents.

2.4. Genotoxicity

No increase in the frequency of sister chromatid exchanges was observed in peripheral lymphocytes from individuals exposed to xylene in occupational (Haglund et al. 1980; Pap and Varga 1987) or experimental settings (Richer et al. 1993).

2.5. Carcinogenicity

Occupational exposure to xylene has been associated with an increased risk of leukemia (Arp et al. 1983; Wilcosky et al. 1984; Anttila et al. 1995); non-Hodgkin's lymphoma (Wilcosky et al. 1984; Anttila et al. 1995); or cancer of the rectum, colon (Siemiatycki 1991; Gérin et al. 1998), or nervous system (Spirtas et al. 1991; Anttila et al. 1995). Despite these associations, however, a number of limitations preclude the usefulness of these data, including small sample sizes, no quantified exposure concentrations, and concurrent exposures to other solvents including benzene.

2.6. Summary

A summary of the effects of xylene exposure on humans is provided in Table 6-4. CNS disturbances after acute and chronic inhalation exposure to xylene include headache, vertigo, nausea, fatigue, irritability, dizziness, impaired concentration, and confusion. Case reports of xylene inhalation have included signs and symptoms such as seizures, unconsciousness and coma, acute pulmonary edema, and transient renal and hepatic impairment. Death occurred due to pulmonary failure after inhalation of mixed xylenes at about 10,000 ppm.

TABLE 6-4 Summary of Controlled Human Exposures to Xylene[a]

Concentration (ppm)	Duration	Isomer	Effect	Reference
110	15 min	Mixed	Intermittent throat irritation (1/6)	Carpenter et al. 1975b
230			Eye irritation (1/7 affected); dizziness (1/7)	
460			Eye irritation (4/6 affected); dizziness (1/6), mild nose/ throat irritation	
690			Eye irritation (4/6 affected); dizziness (4/6, with one having loss of balance), eye/nose/throat irritation	
0, 100, 200, 400	30 min	Mixed	Eye irritation reported, but incidence not statistically significant: (56%, 60%, 70%, 90%, respectively) No nose or throat irritation No change in behavioral tests (performance or cognitive) or respiratory measurements	Hastings et al. 1984
0, 100, 300	70 min	Unknown	No effect on 5 performance tests, heart rate, subjective symptoms Note: exposure via a breathing valve; used menthol to mask odor	Gamberale et al. 1978
300 w/exercise	70 min	Unknown	Significantly decreased performance on short-term memory and reaction time (2/5 tests) Note: exposure via a breathing valve; used menthol to mask odor	Gamberale et al. 1978
100	3 h	Unknown	Significantly affected performance of simple and choice reaction time tests Note: used terpon to mask odor	Dudek et al. 1990
100, 200	3 h or 7h w/ 1 hr break	*m*-, *p*-	No effect on blood pressure, pulse rate, flicker value, or reaction time (total of 23 volunteers)	Ogata et al. 1970
70	4 h	*p*-	No effect on choice reaction time, simple reaction time, short-term memory, heart rate, or subjective symptoms	Olson et al. 1985

200	4 h	*m*-	No adverse effect on VEP, tapping speed, body sway, reaction time, critical flicker fusion	Savolainen et al. 1981; Seppalainen et al. 1983
200	5.5 h	*m*-	No effect on body sway, reaction times, active or quiet sleep; only effect was sleep movements slightly decreased during night after exposure	Laine et al. 1993
100 or 150	7.5 h	*p*-	Mild eye irritation, primarily in person wearing contacts No effect on performance tests	Hake et al. 1981

[a]Exposures separated by a lunch break are not included in this table.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Cats

Four male cats of mixed breed were exposed to air containing a mean measured concentration of mixed xylenes at 9,500 ppm (*p*-xylene, 7.84%; *m*-xylene, 65.01%; *o*-xylene, 7.63%; ethylbenzene, 19.27%) (Carpenter et al. 1975b). Clinical signs during the exposure included salivation, ataxia, tonic and clonic spasms, and anesthesia. All cats were dead within 2 h of exposure. Necropsy failed to reveal any exposure-related histologic lesions.

3.1.2. Rats

Groups of 10 female, Sprague-Dawley rats were exposed to a mixture of xylenes (*o*-, *p*-, and *m*-xylene; percentage of each not provided) by inhalation in a 60-L chamber for 4 h (Lundberg et al. 1986). Xylene concentrations were not provided, but it was stated that they were administered in a geometric series. Solvent concentrations in the chamber were monitored by infrared analysis of a stream of chamber air continuously drawn through an infrared analyzer, and exposure levels were adjusted accordingly. Animals were observed for mortality for 24 h after the start of the exposure. A 4-h 50% lethal concentration (LC_{50}) value of 11,000 ppm (reported as 47,635 mg/m^3; 95% confidence interval, 10,000 to 12,000 ppm) was determined by the Weil method. In another study, rats were exposed to concentrations of 1/32 to 1/2 of the LC_{50} value, and liver damage was assessed by measuring serum levels of sorbitol dehydrogenase activity or by histologic analysis of liver sections. Xylene exposure at these concentrations failed to induce any measurable hepatotoxicity.

Bonnet et al. (1982) exposed groups of 12 male Sprague-Dawley rats to various concentrations of *o*-xylene (98% purity), *m*-xylene (97% purity), or *p*-xylene (98% purity) for 6 h. Vapor concentrations were determined by gas chromatography. Animals were observed for mortality for 14 days after exposure, and LC_{50} values were calculated by the method of Bliss (1938). Individual exposure concentrations and mortalities were not provided in the study. Clinical signs reported for rats exposed to *m*-xylene and *o*-xylene consisted of loss of muscle tone and somnolence, while rats exposed to *p*-xylene also exhibited tremor, shaking, and repetitive movements. The 6-h LC_{50} values with 95% confidence limits were *m*-xylene, 5,984 (5,796 to 6,181); *o*-xylene, 4,330 ppm (4,247 to 4,432); and *p*-xylene, 4,591 ppm (4,353 to 5,049).

Groups of 15 or 16 male albino rats (Harlan-Wistar strain) approximately 5 weeks of age were exposed for 4 h to air containing measured concentrations of mixed xylenes at 580, 1,300, 2,800, 6,000, or 9,000 ppm (*p*-xylene, 7.84%; *m*-xylene, 65.01%; *o*-xylene, 7.63%; ethylbenzene, 19.27%) (Carpenter et al.

1975b; methods are given by Carpenter et al. 1975a). Ten rats per group were used for the LC_{50} determination, while five rats per group were sacrificed after exposure and necropsied. Animals were observed continuously for the first 5 min of exposure, at 15 and 30 min, then at 30-min intervals until 1 and 2 h post-exposure, and daily thereafter. All organs were evaluated grossly at death or sacrifice. Histopathologic evaluation was done of the respiratory tract and liver from three animals (or fewer) per exposure concentration at the end of the 4-h exposure and after 2 days postexposure and of the respiratory tract, liver, kidney, brain, and bone marrow at sacrifice after the 14-day postexposure observation. Mortality results and clinical signs are reported in Table 6-5. A 4-h LC_{50} of 6,700 ppm (95% confidence interval, 5,100 to 8,500 ppm) was calculated by the Thompson method of moving averages. The only findings at necropsy ascribed to treatment were two cases each of pulmonary atelectasis, hemorrhage, and interlobular edema in rats that died after exposure to the highest concentration.

Male Long-Evans rats weighing between 150 and 300 g were exposed to a mixture of *o*-xylene, *m*-xylene, *p*-xylene, and ethylbenzene by inhalation for 4 h and were observed for 14 days for mortality for determination of a 4-h LC_{50} using the method of Litchfield and Wilcoxon (Hine and Zuidema 1970). Information not provided by the study authors included the number of rats per group, the percent of each component in the mixture, the exposure concentration, and whether the LC_{50} calculation was based on nominal or analytic concentrations. The 4-h LC_{50} was 6,350 ppm (confidence limits [not further defined], 4,670 to 8,640 ppm). The authors reported that all deaths occurred during exposure; survivors were comatose upon removal from the chamber but recovered shortly thereafter.

TABLE 6-5 Mortality of Male Rats Exposed to Xylene Vapor for 4 Hours

Concentration (ppm)	Mortality	Other Effects
580	0/10	None observed
1,300	0/10	Poor coordination (slight coordination loss) after 2 h, did not persist after exposure
2,800	0/10	Irritation (not described further), all rats prostrate between 2 and 3.5 h; recovered within 1 h, but coordination remained poor; return to normal following day
6,000	4/10 Died within 3.5 h	Rats prostrate within 30 min; all survivors prostrate but recovered promptly
9,900	10/10 Died within 2.25 h	None stated
6,700		4-h LC_{50}

Source: Carpenter et al. 1975b. Reprinted with permission; copyright 1975, *Toxicology and Applied Pharmacology*.

To determine the effects of xenobiotic interactions with *p*-xylene, adult female CD rats were pretreated with saline, phenobarbital at 75 mg per kg of body weight (mg/kg), chlorpromazine at 15 mg/kg, corn oil, or 3-methylcholanthrene at 20 mg/kg by intraperitoneal injection for three consecutive days before inhalation exposure to *p*-xylene for 4 h for determination of LC_{50} values (Harper et al. 1975). Methods for the xylene exposures were the same as those used for benzene in a previous study (Drew and Fouts 1974). Chamber concentrations were monitored at 30-min intervals by bubbling the air containing the vapor through methanol, and the vapor absorbed in the methanol was measured with a spectrophotometer. The concentrations used in calculating the 4-h LC_{50} are based on the arithmetic means of eight determinations over the 4-h exposure period. Animals were observed for 14 days. The LC_{50} values and the corresponding 95% confidence levels are presented in Table 6-6. Pretreatment with the xenobiotics resulted in minimal changes: phenobarbital increased the LC_{50} by ~20%, while 3-methylcholanthrene and chlorpromazine produced almost comparable LC_{50} values.

Cameron et al. (1938) exposed groups of 10 male and female albino rats or mice by inhalation to *p*-, *m*-, or *o*-xylene (source and purity not specified) at saturation or at one-half, one-fourth, or one-eighth of saturation and reported the resultant mortalities (length of observation not provided). Mortality results are presented in Table 6-7. No treatment-related changes were noted in organs of animals that died after exposure.

Groups of five male albino rats (Harlan-Wistar strain) were exposed to a measured concentration of mixed xylenes at 11,000 ppm for 2 h or for 15, 30, or 60 min (*p*-xylene, 7.84%; *m*-xylene, 65.01%; *o*-xylene, 7.63%; ethylbenzene, 19.27%) (Carpenter et al. 1975a; b). Animals were observed constantly during the exposure—at 0.5, 1, 2, and 4 h postexposure and then once daily for 7 days. Among rats exposed for 2 h, eye irritation was noted immediately at the start of exposure, with prostration present 20 min into the exposure and tremors observed at 45 min. Mortality was observed in 2/5 rats within 66 min and in 4/5 within 80 min. The rat that survived was said to have poor coordination, but the duration of that condition was not stated. No mortality was observed in rats exposed to mixed xylenes at 11,000 ppm for 15, 30, or 60 min. Eye irritation was again noted, and prostration was observed in rats exposed for 30 or 60 min, with full coordination returning 30 min or 2 h postexposure, respectively. The median lethal time was 92 min.

Smyth et al. (1962) reported that 2 h was the maximum exposure time resulting in no mortality within 14 days of exposure to a concentrated vapor of *m*-xylene in albino rats. Inhalation of a nominal concentration of *m*-xylene at 8,000 ppm for 4 h resulted in a mortality of 10/12 within the 14-day observation period.

TABLE 6-6 Mortality of Male Rats Exposed to *p*-Xylene Vapor for 4 Hours After Pretreatment with Xenobiotics

Pretreatment[a]	Dose (mg/kg)	LC_{50} (ppm)	C.I.
Saline	–	4,740	4,520-4,960
Phenobarbital	75	5,810	5,460-6,160
Chlorpromazine	15	4,970	4,700-5,240
Corn oil	–	4,550	3,850-4,750
3-Methylcholanthrene	20	4,960	4,710-5,200

[a]Pretreatment by intraperitoneal injection for 3 days before exposure to xylenes.
Abbreviation: C.I., confidence interval.
Source: Harper et al. 1975. Reprinted with permission; copyright 1975, Kluwer Academic Publishers.

TABLE 6-7 Mortality of Rats Exposed to Xylene Vapor

Isomer	Concentration (ppm)	Length of Exposure (h)	Mortality
o-Xylene	12,250	12	2/10
	6,125	24	8/10
	3,062	24	1/10
	1,531	24	0/10
	1,531	8 × 14 h	0/10
m-Xylene	8,040	12	1/10
	2,010	24	0/10
	1,005	24	0/10
	1,005	8 × 14 h	0/10
p-Xylene	19,650	12	8/10
	4912	24-28	0/10
	2,451	24	0/10
	1,226	8 × 14 h	0/10

Source: Cameron et al. 1938. Reprinted with permission; copyright 1938, *Journal of Pathology & Bacteriology*.

3.1.3. Mice

Bonnet et al. (1979; 1982) exposed groups of 20 to 25 female mice (specific-pathogen-free of stock OF-1) to various concentrations of *o*-xylene (98% purity), *m*-xylene (97% purity), or *p*-xylene (98% purity) for 6 h. Vapor concentrations measured by gas chromatography were 90% to 100% of nominal concentrations. Animals were observed for mortality for 14 days after exposure and LC_{50} values were calculated by the method of Bliss (1938). Individual exposure concentrations and mortalities were not provided in the study; it was stated that mice exposed to *o*-xylene had incidences of delayed mortality between 5 and 10 days postexposure. The 6-h LC_{50} values with 95% confidence limits were *m*-xylene, 5,267 ppm (5,025 to 5,490); *o*-xylene, 4,595 ppm (4,468 to 4,744); and *p*-xylene, 3,907 ppm (3,747 to 4,015).

The concentrations of the xylene isomers required to produce narcosis in white mice were 3,500 to 4,600 ppm for *o*-xylene, 2,300 to 3, 500 ppm for *m*-xylene, and 2,300 ppm for *p*-xylene, while the lethal concentrations were 6,900 ppm for *o*-xylene, 11,500 ppm for *m*-xylene, and 3,500 to 8,100 ppm for *p*-xylene (Lazarew 1929).

Cameron et al. (1938) exposed groups of 10 male and female mice by inhalation to *p*-, *m*-, or *o*-xylene (source and purity not specified) at saturation or at one-half, one-fourth, or one-eighth of saturation and reported the resultant mortalities (length of observation not provided). Mortality results are presented in Table 6-8. No treatment-related changes were noted in organs from animals that died after exposure.

TABLE 6-8 Mortality of Mice Exposed to Xylene Vapor

Isomer	Concentration (ppm)	Length of exposure (h)	Mortality
o-Xylene	12,250	12	2/10
	6,125	24	9/10
	3,062	24	4/10
	1,531	24	0/10
m-Xylene	8,040	12	6/10
	2,010	24	6/10
	1,005	24	0/10
p-Xylene	19,650	12	9/10
	4,912	24-28	0/10
	2,451	24	0/10
	1,226	8 × 14 h	0/10

Source: Cameron et al. 1938. Reprinted with permission; copyright 1938, *Journal of Pathology & Bacteriology*.

3.2. Nonlethal Toxicity

3.2.1. Dogs

Lacrimation developed in male beagles (number of animals not provided) exposed to mixed xylenes at 1,200 ppm for 4 h, while a 4-h exposure to mixed xylenes at 530 ppm had no observable effects (xylene composed of *p*-xylene, 7.84%; *m*-xylene, 65.01%; *o*-xylene, 7.63%; ethylbenzene, 19.27%) (Carpenter et al. 1975b; methods reported by Carpenter et al. 1975a). It is not clear if the concentrations reported by the authors are nominal or were corrected for the 50% to 60% loss that occurred during exposure.

3.2.2. Rats

Flash evoked potentials were assessed in groups of adult male Long-Evans hooded rats after a 4-h exposure to air containing *p*-xylene at 0, 800, or 1,600 ppm (99.8% pure; number of animals not indicated) (Dyer et al. 1988). Exposure to *p*-xylene at 1,600 ppm resulted in a significant depression ($p < 0.003$) in the amplitude of peak N3 depending on time, with a return to control levels 75 min postexposure. The authors postulated that the depression in the N3 peak was the result of increased arousal from the *p*-xylene exposure. This idea is supported by a similar depression in the N3 peak observed after amphetamine administration in rats.

To assess the potential for *p*-xylene exposure to alter serum enzyme activity, groups of female Sprague-Dawley rats were exposed to air containing *p*-xylene at 0, 1,000, 1,500, or 2,000 ppm for 4 h (Patel et al. 1979). Blood samples were collected from the heart from four animals per group immediately after exposure and 24 h after initiation of exposure. By 24 h, increases were observed in the activities of serum glutamic pyruvic transaminase, oxaloacetic transaminase, and 5'-nucleotidase in all exposure groups and of glucose-6-phosphate dehydrogenase, isocitric dehydrogenase, glutathione reductase, and lactic dehydrogenase in the 1,500- and 2,000-ppm groups. In general, the activity of the enzymes was increased in a concentration-related manner. Pseudocholinesterase activity exhibited a concentration-related increase immediately after exposure, but activity returned to control levels 24 h later.

The toxicity of inhaled *p*-xylene was investigated in male Long-Evans rats using a conditioned flavor aversion paradigm, which operates on the premise that pairing the consumption of a novel compound, such as saccharin, with a toxic agent results in a conditioned aversion to the novel flavor (Bushnell and Peele 1988). After acclimation for 1 week, rats were placed on a restricted water schedule of 30 min/day for 10 days. Then rats were given a 0.1% saccharin solution for 30 min instead of water on day 11, followed 30 min later by exposure to *p*-xylene (99.7% pure). Rats were exposed for 4 h to 0, 50, 100, 200, 400, 800, or 1,600 ppm, or for 0.5, 1, 2, 4, or 8 h to *p*-xylene at 0 or 400 ppm. A third

group of rats were exposed to *p*-xylene at 0, 200, or 800 ppm after a 24-h delay after saccharin exposure. After exposure to *p*-xylene, rats were kept on a restricted water schedule but were offered a choice between tap water and a 0.1% saccharin solution. A concentration-related decrease in relative saccharin consumption was observed in all groups exposed to *p*-xylene for 4 h, with maximal aversion occurring in the 800- and 1,600-ppm groups. In rats exposed to *p*-xylene at 400 ppm for various time periods, maximal aversion was noted at 2 to 8 h. Although exposure to *p*-xylene affected saccharin intake, total water consumption was not affected. Rats exposed to *p*-xylene following a 24-h delay after saccharin exposure did not exhibit any aversion to saccharin, demonstrating that there must be close temporal pairing of *p*-xylene and saccharin to produce conditioned flavor aversion.

Groups of eight male Long-Evans hooded rats exposed to *p*-xylene at 1,600 ppm for 4 h/day for 1 to 5 days had improved autoshaping compared with controls as assessed by retraction of a single response lever on a variable 35-second (s) schedule followed by delivery of a food pellet (Bushnell 1989). When the force of the lever was doubled, however, xylene exposure did not facilitate autoshaping compared with controls. Assessment of motor activity after daily exposure indicated that horizontally directed movement in xylene-exposed rats was increased by 30% for the first 15 min of testing, while vertically directed movement was not affected. The activity level of xylene-exposed animals returned to control levels every day, and no difference in activity level of xylene-exposed rats was observed 3.5 h postexposure compared with 0.5 h postexposure. Clinical signs in rats after exposure to *p*-xylene at 1,600 ppm included slight activation, fine tremor, and unsteadiness.

Ghosh et al. (1987) investigated the effects of xylene exposure on fixed-ratio responding in male Fischer 344 (F344) rats. The mixed xylenes comprised *m*-, *p*-, and *o*-xylene with ethylbenzene present as a contaminant; the percent composition was not provided. Xylene exposures and behavioral testing were both carried out in a dynamic exposure behavioral chamber. Chamber concentrations were measured by gas chromatography in 15-min increments. For 6 to 8 weeks, rats were first trained to push a lever 24 times (FR24), which resulted in receiving a 5% sucrose solution. After the initial training, the rats were divided into three groups for further training specific to the experimental protocol of interest. In all three experiments, the recording of the stabilized reinforcement rate for 3 to 4 days before xylene exposure served as the control. In the first group, four rats were further trained for 6.25-h sessions, where lever pressing was rewarded only in the last 15-min period of each hour. After training, rats were successively exposed to graded concentrations of xylenes at 113, 216, and 430 ppm for 2 h each. A concentration-related decrease in the reinforcement rate was observed during the first, third, and fifth hours, while no significant change was observed at the second, fourth, and sixth hours, indicating that tolerance had developed. In the second group, five rats were trained for 2.25-h sessions, where behavioral performance was restricted to the second and fourth 15-min periods of each hour (15 to 30, 45 to 60, 75 to 90, and 105 to 120 min). After training,

rats were exposed for 2 h to xylenes at 114, 212, or 446 ppm, with a minimum of 7 days separating each of the exposures so that tolerance would not develop. A significant decrease in the reinforcement rate was noted at all three concentrations during the 45- to 60-min period (20%, 27%, and 23% decrease in the 114-, 212-, and 446-ppm groups, respectively). Although some decreases in performance were also present in the 212-ppm group at 75 to 90 min (11% decrease) and in the 446-ppm group at 75 to 90 and 105 to 120 min (19% and 17%, respectively), the differences were not statistically significant. In the last group, four rats were trained for 5.25-h sessions in which behavioral performance was limited to the last 15-min period of each hour. Rats were then exposed to xylenes at 98.5 ppm for 5 h. No effects on behavioral performance were observed at any of the time periods during the exposure. The study authors therefore concluded that the minimum effective concentration for xylenes to cause a decrease in reinforcement rate was 113 ppm.

In a similarly designed experiment, Wimolwattanapun et al. (1987) investigated the effect of xylene exposure on intracranial self-stimulation behavior in male F344 rats. The mixed xylenes comprised *m*-, *p*-, and *o*-xylene with ethylbenzene present as a contaminant; the percent composition was not provided. Xylene exposure and behavioral testing were carried out in a dynamic exposure behavioral chamber. Chamber concentrations were measured by gas chromatography in 15-min increments. To study the effects of xylene exposure on intracranial self-stimulation behavior in rats, groups of male F344 rats had bipolar electrodes surgically implanted into the ventral tegmental area of the rats. One week after surgery, rats were trained to press a lever to receive reinforcing electrical stimulation. After the initial training, the rats were divided into three groups for training specific to the experimental protocol of interest. In all three experiments, the recording of the stabilized reinforcement rate for 3 to 4 days before xylene exposure(s) served as the control, and rate of response during exposure was recorded for each 20-min period, with the first and last 20-min periods being control exposures. In the first group, five rats were further trained for 2.67-h periods. After training, rats were exposed to xylene at 102, 192, 419, or 613 ppm for 2 h, with a minimum of 7 days separating the exposures so that tolerance would not develop. Significant decreases ($p < 0.05$) in the rate of response were observed in rats exposed to at least 192 ppm; results are presented in Table 6-9. In the second experiment, no effects on self-stimulation behavior were observed in four rats trained for 4.67-h sessions followed by exposure to 106 ppm for 4 h. The third experiment consisted of exposure of four rats to 444 ppm for 2-h periods for five consecutive days. Results indicated the development of tolerance. Rate of response significantly decreased during the fourth, fifth, and sixth periods on the first day; during all periods on the third day; during the sixth period on the fourth day; and at no time on the fifth day.

To assess the effects of xylene exposure on motility, groups of eight CFY white male rats were exposed by inhalation for 4 h to at least six concentrations each of *m*-xylene (>96% pure), *o*-xylene (>99% pure), or *p*-xylene (>99% pure)

TABLE 6-9 Effect of Xylene Exposure on Self-Stimulation Behavior in Rats

	Responses/20-min period (as percentage of control)							
Concentration (ppm)	–20-0 (control)	1st (0-20)	2nd (20-40)	3rd (40-60)	4th (60-80)	5th (80-100)	6th (100-120)	120-140 (control)
102	112	106	96	105	96	91	98	103
192	100	101	82	75	73*	94	75	90
419	103	98	87	85	61*	75*	76*	84
623	99	87*	81*	84*	89*	85*	87*	99

* Significant decrease ($p < 0.05$) in the rate of response.
Source: Wimolwattanapun et al. 1987. Reprinted with permission; copyright 1987, *Neuropharmacology*.

(individual concentrations not provided) (Molnár et al. 1986). Animals were exposed in a 30-L cylindrical glass chamber, with a solvent-saturated airstream diluted with clean air introduced at the top of the chamber and exhausted at the bottom of the chamber. Concentrations were determined every 30 min by use of an ultraviolet spectrophotometer. Motility during exposure was assessed by means of four electromechanical transducers housed in metal tubes placed perpendicularly throughout the exposure chamber. An electric counter continuously recorded the number of nose touches. The experiments required more than 1 day for completion, and it was not stated if rats were reused for the various exposures. It was stated that exposure to *m*-xylene at 130 to 1,500 ppm and to *p*-xylene at 400 to 1,500 ppm resulted in a concentration-related increase in group motility, while exposure to *o*-xylene at 150 to 1,800 ppm resulted in a slight depression of activity. At higher concentrations, activity decreased in all groups, with the minimum narcotic concentration for the three isomers reported as 2,180 ppm for *o*-xylene, 2,100 ppm for *m*-xylene, and 1,940 ppm for *p*-xylene.

To determine the median effective concentration (EC_{50}) of xylene on rotarod performance, groups of 10 male Wistar rats were exposed to 1,050, 2,030, 2,610, 2,710, 4,130, or 4,700 ppm (reagent grade *o*-, *m*-, *p*-xylene) for 4 h, with a parallel control group of 15 rats exposed to 0 ppm (Korsak et al. 1988). Chamber concentrations were analyzed by gas chromatography. The rotarod test was run both before and immediately after the exposure. All animals survived exposure. The EC_{50} for decreased rotarod performance with a 95% confidence interval was 4,520 ppm (3,800 to 5,390 ppm).

Korsak et al. (1990) exposed groups of 10 male Wistar rats for 6 h to *o*-, *m*-, or *p*-xylene at approximately 3,000 ppm to determine any potential differences in the toxicity of the individual isomers as measured by a rotarod test. Exposures were conducted in a dynamic inhalation chamber (1.3 m^3), where xylene concentrations were measured by gas chromatography. Rats were trained on the rotarod for at least 1 week before exposure. During testing, rotarod performance was measured before and after termination of exposure. The results of the testing given in terms of the number of failures/number of tested animals were as follows: *o*-xylene at an average concentration of 3,027 ppm, 19/20; *m*-

xylene at an average concentration of 3,093 ppm, 6/20; *p*-xylene at an average concentration of 3,065 ppm, 1/20. From this limited experiment, it appeared that *o*-xylene was a more potent CNS depressant in rats than the other two isomers.

In a later experiment in which only *m*-xylene was tested, Korsak et al. (1993) exposed groups of 8 to 10 male Wistar rats to different concentrations of *m*-xylene in a dynamic inhalation chamber for 4 h immediately followed by rotarod testing or measurement of spontaneous motor activity by an actometer for 1 h postexposure. Xylene concentrations were measured in the exposure chamber in 30-min increments by gas chromatography. Exact exposure concentrations were not provided, but graphic representation of data showed *m*-xylene exposure concentrations of about 500, 1,000, 1,500, 2,000, or 3,000 ppm. The effect of exposure on spontaneous motor activity was biphasic, with lower concentrations (up to 2,000 ppm) resulting in increased motor activity and higher concentrations (3,000 ppm) resulting in decreased motor activity. The 4-h EC_{50} for *m*-xylene effects on rotarod performance was 1,982 ppm (95% confidence interval, 1,530 to 2,565 ppm). This concentration is lower than that used in the previous Korsak et al. (1990) experiment, in which the toxicity of the individual isomers was assessed in rats by comparing rotarod performance after exposure to 3,000 ppm for 6 h.

To assess erythrocyte fragility after exposure to xylene, groups of five male albino rats (Harlan-Wistar strain) were exposed to air containing mixed xylenes in metered concentrations of 0 or 15,000 ppm (64 mg/L) (corrected concentration approximately 8,800 ppm: composed of *p*-xylene, 7.84%; *m*-xylene, 65.01%; *o*-xylene, 7.63%; ethylbenzene, 19.27%) for 45 min (Carpenter et al. 1975a,b). The rats were killed after exposure, and their blood was collected. Erythrocyte fragility was determined by placing one drop of blood in a tube with different concentrations of saline to determine the concentration of saline causing initial and complete hemolysis. Hemolysis in xylene-exposed rats was comparable to that in the concurrent controls. No increase in erythrocyte fragility was observed in xylene-exposed rats compared with controls.

3.2.3. Mice

Groups of six male Swiss OF_1 mice inhaled air containing at least four different concentrations of *o*-xylene to determine the concentration of *o*-xylene associated with a 50% decrease in respiratory rate (RD_{50}) (de Ceaurriz et al. 1981). The test concentrations were not stated, and, although it was stated that xylene was of a high purity, the actual purity was not provided. Animals were exposed in a 200-L exposure chamber with adjustable air flow. The air concentration of *o*-xylene in the test chamber was determined by sweeping a sample loop through the cell atmosphere and analyzing the sample by gas chromatography. Respiratory rate was measured with a body plethysmograph. Recordings were made for 10 min before exposure, and then the mice were placed in an exposure cell with a predetermined concentration of *o*-xylene until the maximum

decrease in respiration was reached. Exposure was generally for only 5 min. On the basis of results from these exposures, the RD_{50} for *o*-xylene was 1,467 ppm.

Korsak et al. (1988) determined the RD_{50} for mixed xylenes (reagent grade *o*-, *m*-, *p*-xylene; further details not provided), toluene, and a 50:50 (vol/vol) mixture in groups of two to four BALB/c male mice. For determination of the xylene RD_{50}, mice were exposed to xylene at 2,600, 4,000, 4,600, or 7,000 ppm, and their respiratory rates were measured with a body plethysmograph continuously before exposure, during 6 min of exposure, and 2 to 3 min after termination of exposure. The RD_{50} for mixed xylenes was 2,440 ppm.

Korsak et al. (1993) also determined the RD_{50} for *m*-xylene, *n*-butyl alcohol, and the 50:50 mixture (supplied by Reachim and the Polish Chemical Reagent company, further information not provided) in groups of 8 to 10 BALB/c male mice with a body plethysmograph. Actual test concentrations studied were not provided. The RD_{50} for *m*-xylene was 1,361 ppm. In a second paper, Korsak et al. (1990) exposed groups of six BALB/c male mice to *p*-, *o*-, or *m*-xylene at 3,000 ppm, and the respiratory rate was measured with a body plethysmograph continuously before exposure, during 6 min of exposure, and 3 min after termination of exposure. The maximum reductions in respiratory rate were measured during the first minute of exposure and were 54%, 46%, and 43% of controls for the mice exposed to *p*-xylene, *o*-xylene, and *m*-xylene, respectively.

Carpenter et al. (1975a,b) exposed Swiss-Webster male mice to air containing measured concentrations of mixed xylenes (*p*-xylene, 7.84%; *m*-xylene, 65.01%; *o*-xylene, 7.63%; ethylbenzene, 19.27%) for 1 min and then measured respiratory rate during a 15-min postexposure period. A 50% or greater decrease in respiratory rate was observed in 5/5 rats at 12,000 ppm, 4/6 rats at 6,500 ppm, 2/6 rats at 2,500 ppm, and 2/6 rats at 1,300 ppm. A 50% reduction in respiratory rate was not observed in any of the rats exposed to 460 ppm.

A functional observational battery (FOB) was adapted to mice to evaluate acute behavioral effects of alkylbenzenes (Tegeris and Balster 1994). Groups of eight adult male CFW albino mice inhaled air containing *m*-xylene (98% purity) at 0, 2,000, 4,000, or 8,000 ppm for 20 min under static conditions. After individual mice were placed into 29-L glass jars sealed with a lid, xylene was injected onto a filter paper in the jar, with a fan blade in the chamber distributing the vapors equally. Analysis of air by infrared spectrometry confirmed nominal vapor concentrations and demonstrated that maximal concentrations were reached within 3 min of fan activation and remained constant throughout exposure. Within 10 to 15 s after exposure, mice were removed from the jar and evaluated according to a complete FOB.

During the last 2 min of the exposure, concentration-related, statistically significant effects were observed including decreased arousal and rearing, abnormal posture, altered palpebral closure, and disturbances of gait (Tegeris and Balster 1994). Because the statistical significance of the effects was reported at two or more doses, it is not clear whether the changes were limited to the 4,000- and 8,000-ppm groups or extended to the 2,000-ppm group. The authors stated that exposure to all concentrations including 2,000 ppm resulted in decreased

rearing. After exposure, the FOB revealed statistically significant reductions among the 8,000-ppm group in the percentage of animals with a successful inversion in the inverted screen test, in the percentage of animals with a normal ranking in righting reflex, and in mean forelimb grip strength. Statistically increased mean hindlimb foot splay was observed in all exposure groups. Exposure to xylene also resulted in decreased responsiveness to stimulus presentation. Because the purpose of the study was to qualitatively compare six alkylbenzenes, no attempt was made to determine minimally effective concentrations.

The effects of the individual xylene isomers and a commercial xylene mixture on operant responding and motor performance were assessed in CD-1 male albino mice (Moser et al. 1985). All exposures occurred in a 29-L glass chamber under static conditions, with measurements of chamber air by an infrared spectrophotometer confirming that solvent concentration remained stable throughout the exposure. To measure operant response after xylene exposure, 15 mice were feed-deprived throughout the study. The mice were tested in three squads, with the order of each isomer counterbalanced among the squads and a week separating the testing of each isomer. The xylene mixture was tested during the last week for all squads. Mice were exposed on Tuesday through Friday of each week to air or ascending xylene concentrations of 500, 800, 1,400, 2,400, 4,000, 5,000, or 7,000 ppm for 30 min. Immediately after exposure, mice were placed in an operant chamber. Before exposure, they were trained to lever-press during daily 15-min sessions, followed by a differential-reinforcement-of-low-rates 10-s schedule. Motor performance was assessed by measuring the performance of mice in an inverted screen test study after exposure to the solvent. Groups of 12 mice (two squads of six mice) were exposed to at least three concentrations producing between 0% and 100% effects (2,000 to 7,000 ppm). It is assumed that the exposure duration was 30 min, but it was not stated definitively in the paper.

The results of the operant studies indicated that the order of exposure to the xylene isomers or mixture had no effect on the outcome (Moser et al. 1985). The minimally effective concentration for disruption of operant performance was 1,400 ppm for all isomers, with an EC_{50} (concentration producing half-maximal decreases in response rate) of 6,176, 5,179, and 5,611 ppm for *m*-xylene, *o*-xylene, and *p*-xylene, respectively. The operant response was biphasic, with concentrations of 1,400 to 2,400 ppm producing increased rates of response, and a concentration of 7,000 ppm suppressing the response rate and producing gross ataxia and prostration. The minimally effective concentrations for the inverted screen test were 3,000 ppm for *m*- and *o*-xylene and 2,000 ppm for *p*-xylene, while the EC_{50} values for performance on the inverted screen test were 3,790, 3,640, and 2,676 ppm for *m*-xylene, *o*-xylene, and *p*-xylene, respectively. Motor ability was recovered 5 to 15 min after exposure. The study authors concluded that there was no consistent, significant difference in the potency of the individual isomers. While *o*-xylene exhibited increased potency on operant behavior, *p*-xylene reduced motor performance.

3.3. Developmental and Reproductive Effects

In a one-generation reproduction study, groups of male and female CD rats were exposed to mixed xylenes at 0, 60, 250, and 500 ppm (Groups I, II, III, and IV, respectively; technical grade xylene: 2.4% toluene, 12.8% ethylbenzene, 20.3% *p*-xylene, 44.2% *m*-xylene, 20.4% *o*-xylene) by inhalation for 6 h/day, 5 days/week, for 131 days before mating (Bio/dynamics Inc. 1983). Exposure continued in the females during gestation days (GD) 1 to 20 and throughout lactation days 5 to 20. Two additional 500-ppm groups were included: only the males were exposed in Group V, and only the females were exposed in Group VI. Potential pup exposure to xylenes was only through milk. No definite, exposure-related adverse effects were noted in F_0 adults or pups. Although marginal reductions in pup body weight in exposed groups were observed, the changes were not considered adverse because the concurrent control group had an elevated mean pup body weight associated with a smaller mean litter size (mean number of live pups per litter: 9.6, 11.8, 12.5, 12.4, 10.8, and 11.8 for Groups I to VI, respectively). No decrease in pup body weight was observed in Group VI, in which dams were exposed to the same concentration of xylene for the same period of time as dams in Group IV.

To assess potential developmental toxicity, one-half of the Group I F_0 females (20 females; control group) and Group IV F_0 females (12 females; mixed xylenes at 500 ppm by inhalation for 6 h/day, 5 days/week, for 131 days before to mating and during GD 1 to 20) were killed on GD 21 (Bio/dynamics Inc. 1983). No exposure-related signs of maternal toxicity were observed. No statistically significant differences were noted between treated and control groups for mean number of corpora lutea, implantations, resorption sites, live fetuses, mean percentage of live fetuses/implants, or fetal sex ratios. No definitive treatment-related external, visceral, or skeletal malformations or variations were observed. The report stated that fetuses exposed to high doses had a slightly higher incidence of unossified sternebrae and incompletely ossified cervical vertebral transverse processes, but the data were provided in terms of fetal incidence instead of litter incidence. Mean fetal body weight on GD 21 was marginally but statistically reduced in female offspring from Group IV (93% of controls); however, male fetal body weight was comparable to that of controls. This marginal reduction in body weight in female offspring is difficult to assess because male fetal weight was unaffected.

No signs of maternal or developmental toxicity were observed after exposure of pregnant CRL: COBS CD (SD) BR rats to xylene at 0, 100, or 400 ppm (52% *m*-xylene, 11% *o*-xylene, 0.31% *p*-xylene, 36% ethylbenzene) for 6 h/day on GD 6 to 15 (Litton Bionetics 1978a). The no-observed-adverse-effect level (NOAEL) is therefore ≥400 ppm.

To evaluate the effects of prenatal xylene exposure on postnatal development, pregnant (Mol:WIST) rats were exposed by inhalation to xylene at 0 or 500 ppm (19% *o*-xylene, 45% *m*-xylene, 20% *p*-xylene, 15% ethylbenzene) 6 h/day, on GD 7 to 20 and were allowed to deliver (Hass et al. 1995). From each

litter, two males and two females were kept for behavioral testing, one male and one female were kept in standardized housing and left undisturbed other than feeding and taking body weight measurements until 3 months of age when they were tested in the Morris water maze test (tests learning and memory). One male and one female were kept in enriched housing (cages contained various toys) and tested for rotarod, open field, and Morris maze performance at about 3 months of age. The only possible effect observed was that offspring from xylene-exposed rats raised in the standard housing had impaired performance in the Morris maze test compared with controls. Testing at 12 weeks showed a nonsignificant trend ($p = 0.059$) for increased latency for finding the platform at the beginning of the learning test. At 16 weeks, these rats required significantly more time to find a platform hidden in the center of the pool. Further analysis revealed the effect was limited to the female offspring, which had an increased swimming length (took a longer route to reach the platform), while swim speed was unaffected. Offspring from xylene-exposed rats raised in the enriched environment showed no difference in the Morris maze test compared with controls.

In a study designed to investigate the persistence of the decreased Morris water maze test performance of the offspring from the xylene-exposed (Mol:WIST) female rats, the female offspring raised in standard housing were also evaluated at 28 and 52 weeks (Hass et al. 1997). At 28 weeks, increased latency for finding a platform that was moved to a new position was observed in the female offspring from exposed rats during the first trial of a testing block. The next two trials resulted in similar latency in exposed but not control rats. The increased latency again corresponded to increased swimming distance. No significant differences were observed for other testing situations in the Morris maze test. At 55 weeks, no statistically significant differences were observed between groups.

The Hass et al. (1995, 1997) studies found that prenatal exposure to xylenes affected the performance of female offspring in the Morris water maze test: female offspring took longer to find the platform. While swim length increased, swim speed was unaffected, indicating a cognitive rather than motor effect. These studies are limited, however, in that a concentration response is lacking because only one concentration was tested. Furthermore, no clear effect was observed in any of the other neurologic tests.

Groups of 36 pregnant, female Wistar rats were exposed to technical grade xylene at 0 or 200 ppm (exact composition not provided) for 6 h/day during GD 6 to 20 (Hass and Jakobsen 1993). On GD 21, two-thirds of the dams were killed and used to assess developmental toxicity, and one-third of the dams were allowed to deliver and developmental milestones and rotarod performance were assessed in eight offspring (four males and four females) from each litter. No signs of maternal toxicity were observed in any of the exposed dams. The only effect noted in fetuses from xylene-treated dams was an increased incidence of delayed ossification of the os maxcillare in the skull, with 18/26 exposed litters affected versus 2/22 control litters. In the postnatal study, statistically decreased rotarod performance was observed in female pups on postnatal days 22 and 23

and in male pups on postnatal day 23. The Hass and Jakobsen (1993) study is limited in that only one exposure concentration was tested and only a limited battery of behavioral tests was used. Hass et al. (1995) conceded that the investigators were not blind to the exposure status of the animals.

Exposure of pregnant Sprague-Dawley rats to *p*-xylene at 800 or 1,600 ppm (3,500 or 7,000 mg/m^3; 99% pure) on GD 7 to 16 failed to influence litter size or pup weights at birth or on postnatal day 3; CNS development as measured by the acoustic startle response on postnatal days 13, 17, 21, and 63 or the figure-eight maze activity evaluated on postnatal days 22 and 65; or the growth rate of the pups (Rosen et al. 1986). The only effect of exposure was a significant reduction in maternal body weight gain in the dams at 1,600 ppm (74% of controls).

To investigate the effect of xylene inhalation on the liver of pregnant and nonpregnant rats and pups of exposed litters, pregnant Wistar rats were exposed to xylenes at 2,600 ppm (11,284 mg/m^3) (purity and composition not stated) for 8 h/day on GD 6 until term (GD 21) (Kükner et al. 1997-1998). Nonpregnant female rats were exposed to xylenes at 2,600 ppm for the same period, and a control group of pregnant rats inhaled clean air (not stated if nonpregnant controls were also included). Biochemical analyses of the livers from pregnant rats exposed to xylene found minimal increases in aspartate aminotransferase (18%), alanine aminotransferase (19%), alkaline phosphatase (17%), and arginase (63%) activity. Electron microscopic evaluation of pregnant and nonpregnant rat liver tissue revealed mitochondria that concentrated near the periphery of hepatocytes and nuclei, increased numbers of lysosomes, and expanded smooth endoplasmic reticulum. In fetal liver from exposed litters, findings included expanded smooth endoplasmic reticulum, structurally deformed mitochondria, and granular endoplasmic reticulum. No structural defects were observed in the kidneys or pancreas from exposed pregnant or nonpregnant rats or from fetuses recovered from xylene-exposed litters.

A number of other developmental toxicity studies were identified in the literature but were limited by several factors: composition and purity of the tested xylenes was not stated, values for the toxicity end points were not provided, fetal instead of litter incidences were reported, or inadequate sample sizes were available (Hudák and Ungváry 1978; Ungváry et al. 1980; Mirkova et al. 1983; Ungváry and Tátrai 1985).

3.4. Genotoxicity

The genotoxicity of commercial xylene and all three individual isomers has been extensively tested and the results have generally been consistently negative. All studies evaluated by the GENETOX panel and cited in the GENETOX database were negative except for one study for which no conclusion could be drawn (GENETOX 1992). Xylene was not mutagenic in bacterial

test systems with strains of *Salmonella typhimurium* (Florin et al. 1980; Bos et al. 1981; NTP 1986) and *Escherichia coli* (McCarroll et al. 1981) or in cultured mouse lymphoma cells (Litton Bionetics 1978b). Xylene failed to induce chromosomal aberrations or sister chromatid exchanges in cultured Chinese hamster ovary cells (Anderson et al. 1990) or cultured human lymphocytes (Gerner-Smidt and Friedrich 1978), chromosomal aberrations in rat bone marrow (Litton Bionetics 1978b), micronuclei in mouse bone marrow (Mohtashamipur et al. 1985), or sperm head abnormalities in rats (Washington et al. 1983). Technical grade xylene, but not *o*- and *m*-xylene, was weakly mutagenic in *Drosophila* recessive lethal tests (Donner et al. 1980).

3.5. Carcinogenicity

No studies were found in the published literature on the carcinogenic potential of inhaled xylene in animals.

In a National Toxicology Program (NTP 1986) chronic toxicity and carcinogenesis bioassay, groups of 50 male and 50 female F344 rats and 50 male and 50 female B6C3F1 mice were administered mixed xylenes (60% *m*-xylene, 13.6% *p*-xylene, 17.0% ethylbenzene, and 9.1% *o*-xylene) in corn oil by gavage at doses of 0, 250, or 500 mg/kg/day (rats) and 0, 500, or 1,000 mg/kg/day (mice) for 5 days/week for 103 weeks. Histopathologic examination of the rats revealed an increased incidence of interstitial cell tumors in the testis of high-dose males after survival-adjusted analysis, but this increase was believed to be a consequence of high-dose animals dying between weeks 62 and 92. The overall incidence of interstitial cell tumors between groups was comparable (43/50, 38/50, and 41/49 for the control, low-dose, and high-dose groups, respectively). Therefore, the marginal increase in this tumor type was not ascribed to treatment. The National Toxicology Program (NTP 1986) reported no significant nonneoplastic or neoplastic effects in male or female mice.

Maltoni et al. (1983, 1985) exposed groups of 40 male and 40 female Sprague-Dawley rats to xylene at 0 or 500 mg/kg (mix of *o*-, *p*-, and *m*-xylenes; proportion of each isomer not stated) in olive oil orally by gavage 4 to 5 days/week for 104 weeks, followed by discontinuation of dosing to study termination at 141 weeks. Although Maltoni et al. reported an increase in the overall number of malignant tumors in treated males (14/40 versus 11/50 for controls) and females (22/40 versus 10/50 for controls), further results and explanation were not provided.

IARC (1999) has concluded that evidence for the carcinogenicity of xylene in humans or in experimental animals is inadequate and therefore stated that xylene is not classifiable as to carcinogenicity in humans (Group 3). The EPA (2003) has not classified xylenes as to carcinogenicity because data are inadequate to assess their carcinogenic potential.

3.6. Summary

Xylene is an anesthetic solvent that may cause narcosis and death at sufficiently high atmospheric concentrations. In rats and mice, 4-h LC_{50} values ranging from 3,907 to 11,000 ppm have been reported (see Table 6-10). At lower concentrations, CNS disturbances and irritation are evident (see Table 6-11). No indication of consistent developmental or reproductive signs of toxicity was documented in the available literature. Commercial xylene and the three individual isomers failed to demonstrate any evidence of genotoxicity. Xylenes are currently not classified as to carcinogenicity by IARC (1999) or the EPA (2003).

TABLE 6-10 Summary of Lethal Xylene Inhalation Data in Laboratory Animals

Concentration (ppm)	Duration (h)	Isomer	Mortality and Other Effects	Reference
Cat				
9,500	2	Mixed	Killed all 4 cats	Carpenter et al. 1975b
Rat				
6,700	4	Mixed	LC_{50}	Carpenter et al. 1975b
6,350	4	Mixed	LC_{50}	Hine and Zuidema 1970
4,645	4	*p*-	LC_{50}	Harper et al. 1975
11,000	4	Mixed	LC_{50}	Lundberg et al. 1986
5,984	6	*m*-	LC_{50} *m*-xylene	Bonnet et al. 1982
4,330	6	*o*-	LC_{50} *o*-xylene	
4,591	6	*p*-	LC_{50} *p*-xylene	
1,531	24	*o*-	Highest no-effect level for death	Cameron et al. 1938
2,010	24	*m*-		
4,912	24-28	*p*-		
Mouse				
5,267	6	*m*-	LC_{50} *m*-xylene	Bonnet et al. 1979, 1982
4,595	6	*o*-	LC_{50} *o*-xylene	
3,907	6	*p*-	LC_{50} *p*-xylene	
1,531	24	*o*-	Highest no-effect level for death	Cameron et al. 1938
1,005	24	*m*-		
4,912	24	*p*-		

TABLE 6-11 Summary of Nonlethal Xylene Inhalation Data in Laboratory Animals

Concentration (ppm)	Duration (h)	Isomer	Effects	References
Dog				
530	4	Mixed	No effect level	Carpenter et al. 1975b
1,200	4	Mixed	Lacrimation	
Rat				
580	4	Mixed	No effect level	Carpenter et al. 1975b
1,300	4	Mixed	Poor coordination after 2 h, recovered postexposure	
2,800	4	Mixed	Irritation; rats prostrate within 2.5-3 h into exposure; recovered within 1 h, but poor coordination until following day.	
1,600	4	*p*-	Changes in flash evoked potential suggest increased arousal	Dyer et al. 1988
2,100	4	*m*-	Minimum narcotic concentration	Molnár et al. 1986
2,180	4	*o*-		
1,940	4	*p*-		
800, 1,600	4	*p*-	Induced flavor aversion	Bushnell and Peele 1988
1,600	4	*p*-	Hyperactivity, fine tremor, unsteadiness	Bushnell 1989
113	2	Mixed	Minimum effective concentration for decreased reinforcement rate	Ghosh et al. 1987

(Continued)

TABLE 6-11 Continued

Concentration (ppm)	Duration (h)	Isomer	Effects	References
98.5	5	Mixed	No effect of reinforcement rate	Ghosh et al. 1987
192	2	Mixed	Lowest concentration resulting in decrease in the rate of response for self-stimulation behavior	Wimolwattanapun et al. 1987
4,520	4	Mixed	EC_{50} for rotarod performance	Korsak et al. 1988
1,982	4	*m*-	EC_{50} for rotarod performance	Korsak et al. 1993
Mouse				
1,467		*o*-	RD_{50}	de Ceaurriz et al. 1981
1,361		*m*-	RD_{50}; not recommended strain of mice	Korsak et al. 1993
2,440		Mixed	RD_{50}; not recommended strain of mice	Korsak et al. 1988
2,000, 4,000, 8,000	0.33 (static)	*m*-	Increased mean hindlimb foot splay, decreased rearing	Tegeris and Balster 1994
3,790	0.5 (static)	*m*-	EC_{50} for inverted screen test	Moser et al. 1985
3,640	0.5 (static)	*o*-		
2,676	0.5 (static)	*p*-		
6,176	0.5 (static)	*m*-	EC_{50} for disruption of operant performance	Moser et al. 1985
5,179	0.5 (static)	*o*-		
5,611	0.5 (static)	*p*-		

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Pulmonary retention of inhaled xylene in humans has been reported to range between 49.8% and 72.8% (ATSDR 2007). No difference in retention has been observed among the individual isomers (Sedivec and Flek 1976) or between sexes (Senczuk and Orlowski 1978), but systemic uptake is increased by exercise (Astrand et al. 1978; Gamberale et al. 1978). After uptake from the lungs, xylene is distributed by the circulation to the peripheral tissues. The values for the human blood-air partition coefficient (PB) are 26.4, 31.9, and 32.5 for *m*-xylene; 31.1, 35.2, and 34.9 for *o*-xylene; and 37.6, 39.0, and 44.7 for *p*-xylene (Sato and Nakajima 1979; Gargas et al. 1989; Pierce et al. 1996), and the values for the rat PB are 46.0 for *m*-xylene, 44.3 for *o*-xylene, and 41.3 for *p*-xylene (Gargas et al. 1989). In human blood, xylene is associated primarily with serum proteins (Riihimaki et al. 1979). Distribution to human adipose tissue has been estimated to represent 3.7% to 10% of total uptake after inhalation (Engstrom and Riihimaki 1979; Astrand 1982). Inhalation exposure of mice and rats to radiolabeled xylene demonstrated that xylene is rapidly taken up from the lungs by the blood and immediately distributed to the kidneys, brain, subcutaneous body fat, bone marrow, spinal cord and spinal nerves, liver, and nasal mucosa; it is rapidly eliminated from these tissues with the exception of fat (Carlsson 1981; Bergman 1983; Kumarathasan et al. 1997). Ghantous et al. (1990) reported accumulation of xylene metabolites, primarily methylhippuric acid, in the nasal mucosa and olfactory bulb of the brain in mice after inhalation of radiolabeled *p*-xylene. Xylene has also been detected in the placenta, fetus, and amniotic fluid after maternal exposure, but the concentrations in fetal tissues were much lower than those in the maternal tissues (Ungváry et al. 1980; Ghantous and Danielsson 1986).

The primary metabolic pathway in humans is side-chain dehydroxylation by hepatic mixed-function oxidases to toluic acids (see Figure 6-1). The toluic acids are then conjugated with glycine to form methylhippuric acid isomers and excreted in urine. The methylhippuric acid isomers are produced almost exclusively in humans, with urine accounting for elimination of 95% to 97% of the absorbed dose in humans (Sedivec and Flek 1976; Riihimaki et al. 1979; Engstrom et al. 1984). Less than 10% of the absorbed dose is excreted unchanged by the lungs or kidneys (Sedivec and Flek 1976; Riihimaki et al. 1979) or as minor metabolites including urinary xylenols (Sedivec and Flek 1976; Riihimaki et al. 1979; Engstrom et al. 1984), toluic acid glucuronides (Ogata et al. 1979, 1980), or mercapturic acid (Norström et al. 1988). Miller and Edwards (1999) found evidence that of the three xylene isomers, *m*-xylene is preferentially metabolized to methylhippuric acid in the presence of the other two isomers, regardless of the isomer composition. The relevance of this finding in assessing the toxicity of the individual isomers is not known at this time.

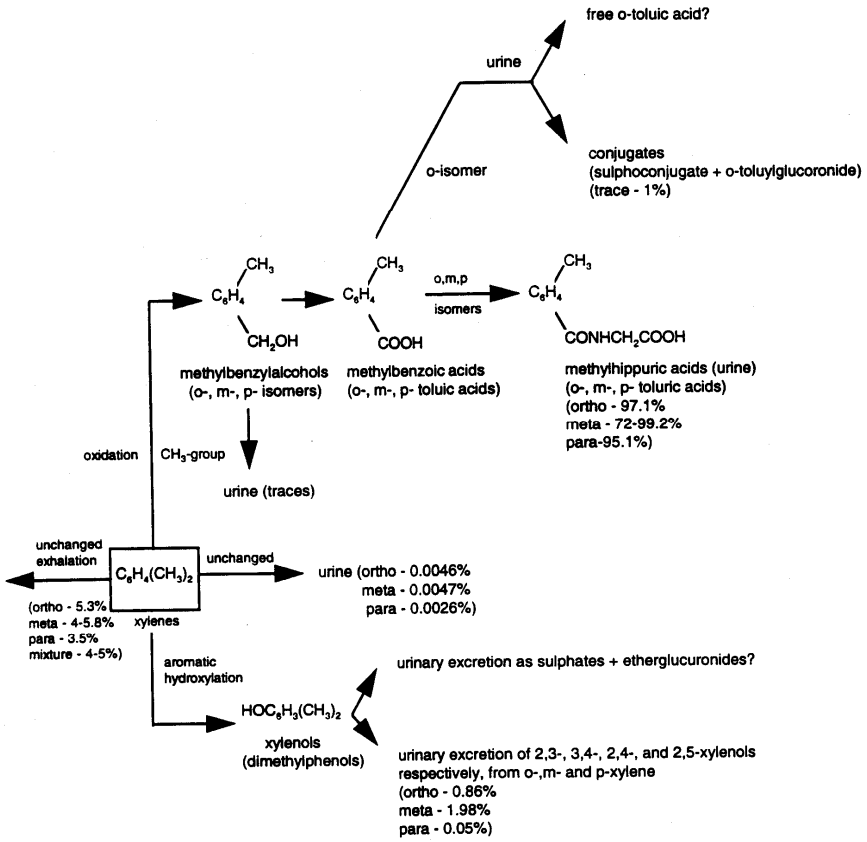


FIGURE 6-1 Metabolic scheme for xylenes in humans. Source: ATSDR 2007.

Metabolism of xylenes in common laboratory animals also proceeds via hepatic side-chain dehydroxylation by mixed function oxidases to toluic acids. Further metabolism depends on species and isomer composition, with fluctuations occurring primarily in the ratio of urinary methylhippuric acid and toluic acid glucuronides (Bray et al. 1949; Ogata et al. 1980; Tardif et al. 1989). It has been proposed that the differences observed between humans and animals in xylene metabolism may be due to differences in the size of the doses administered to each: the larger doses received by animals may saturate the glycine-conjugation pathway (Figure 6-1) (ATSDR 2007).

In humans, excretion of xylenes after inhalation is rapid and occurs almost exclusively as urinary methylhippuric acid isomers with a minor amount as toluic acid glucuronides (Ogata et al. 1970; Senczuk and Orlowski 1978; Riihimaki et al. 1979; Ogata et al. 1980; Engström et al. 1984). Only a minor amount (4% to 5%) of absorbed xylene is excreted unchanged by the lungs (Sedivec and

Flek 1976; Riihimaki et al. 1979). Riihimaki et al. (1979) estimated that human excretion of xylene in air and urine has an initial half-life of 1 h, followed by a slow phase with an estimated half-life of 20 h. In general, a linear correlation has been found between the intensity of xylene exposure and the amount of methylhippuric acid isomers excreted in the urine (Lundberg and Sollenberg 1986; Imbriani et al. 1987; Kawai et al. 1991, 1992; Inoue et al. 1993).

4.2. Mechanism of Toxicity

Xylene exposure of humans and common laboratory animals can result in nervous system disturbance. CNS effects in humans after acute and chronic inhalation exposure to xylene include headache, vertigo, nausea, fatigue, irritability, dizziness, impaired concentration, and confusion (Carpenter et al. 1975b; Hipolito 1980; Klaucke et al. 1982). Case reports of individuals exposed to high concentrations of xylenes by inhalation, ingestion, or intravenous injection have reported severe respiratory effects including respiratory failure (Morley et al. 1970; Recchia et al. 1985; Abu Al Ragheb et al. 1986; Sevcik et al. 1992). The respiratory effects were most likely a secondary response to depression of the respiratory center of the brain. Nonlethal effects after exposure to high concentrations of xylenes (~10,000 ppm) include unconsciousness, slurred speech, and ataxia (Morley et al. 1970). Controlled acute inhalation exposure in human males yielded mixed results after neurobehavioral testing. A number of studies found that exposure to *p*- or *m*-xylene concentrations ranging from 70 to 400 ppm for up to 4 h either failed to affect the performance of subjects in neurobehavioral testing (Olson et al. 1985) or actually improved performance (Savolainen et al. 1981, 1985b; Laine et al. 1993). Other studies found correlations between acute exposure to *m*-xylene at concentrations ranging from 64 to 400 ppm for up to 4 h and impaired performance (Gamberale et al. 1978; Savolainen and Linnavo 1979; Savolainen et al. 1979b, 1980; Savolainen and Riihimaki 1981; Seppalainen et al. 1983; Savolainen et al. 1984, 1985a; Seppalainen et al. 1989; Dudek et al. 1990; Seppalainen et al. 1991). Some studies evaluating the effects of acute exposure to *m*-xylene have indicated the development of tolerance in exposed subjects (Savolainen et al. 1980; Savolainen and Riihimaki 1981).

Signs of CNS toxicity after acute exposure to xylenes were also reported in animals. Preanesthetic effects associated with acute exposure to high concentrations of xylenes include poor coordination and prostration (Carpenter et al. 1975b), increased hindlimb foot splay (Tegeris and Balster 1994), reduced performance on the inverted screen test (Moser et al. 1985) and rotarod (Korsak et al. 1988; 1993), and disrupted operant performance (Moser et al. 1985). CNS effects after exposure to lower concentrations of xylenes include changes in flash evoked potentials (Dyer et al. 1988), induced flavor aversion (Bushnell and Peele 1988), decreased reinforcement rates of fixed-ratio responding (Ghosh et al. 1987), decreased rates of response for self-stimulation behavior (Wimolwat-

tanapun et al. 1987), and facilitated autoshaping (Bushnell 1989). Evidence of tolerance was also reported in animals (Ghosh et al. 1987; Wimolwattanapun et al. 1987).

The low molecular weight and lipophilic nature of xylenes allow the solvent to readily cross the blood-brain barrier. Studies investigating the distribution of radiolabeled xylenes after inhalation confirmed high concentrations of xylene in the brain and central and peripheral nervous systems immediately after exposure, with elimination often occurring by 1 h postexposure (Carlsson 1981; Bergman 1983; Ghantous and Danielsson 1986; Kumarathasan et al. 1997). The transient nature of many of the xylene-induced nervous system disturbances is likely due to the rapid elimination of xylene. The precise molecular mechanism by which xylenes affect the nervous system is not known. An in vitro study using human and rat cell membranes demonstrated that xylene and other solvents with anesthetic properties could bind in hydrophobic pockets in integral cell membrane proteins, thereby altering the properties of integral enzymes (Tahti 1992). Others found that xylene exposure affected the enkephalinergic neuromodulatory system (de Gandarias et al. 1995), catecholamine neurotransmission by altering levels of dopamine and noradrenaline (Andersson et al. 1981), and levels of brain acetylcholine and glutamine (Honma et al. 1983). Xylene exposure reduced transport of cellular materials to axons and nerve ending regions in rats (Padilla and Lyerly 1989), affected microsomal superoxide dismutase activity in the brain of rats (Savolainen et al. 1979a), and resulted in findings compatible with astrogliosis in gerbils (increased brain concentrations of glial fibrillary acidic protein, S-100 protein, and DNA) (Rosengren et al. 1986). Xylene exposure did not influence neutral or basic aminopeptidase activities in the brains of rats (de Gandarias et al. 1993).

Data demonstrating the hepatoxicity of xylene are limited. Human data were primarily limited to case reports. Morley et al. (1970) reported an accidental exposure to xylene at approximately 10,000 ppm. The autopsy of a worker who died revealed hepatic congestion with swelling and vacuolization of cells in the centrilobular areas. Two other xylene-exposed workers who survived had only slight hepatic impairment as indicated by a rise in serum transaminase activity over 48 h after exposure, after which the enzyme activity returned to normal levels. Hepatic changes in rats sometimes followed subchronic oral or inhalation exposure to xylenes and may be consistent with an adaptative response (Tátrai and Ungváry 1980; Tátrai et al. 1981; Ungváry 1990).

Developmental toxicity in animals has generally been observed only at doses or concentrations similar to or exceeding those resulting in maternal toxicity. Two studies were found investigating the potential mechanism for xylene-induced developmental toxicity (developmental retardation and death). In a study investigating the role of maternal sex steroid production and metabolism in *p*-xylene embryotoxicity, Ungváry et al. (1981) reported that exposure of pregnant rats to *p*-xylene at 690 ppm (3,000 mg/m^3) on GD 10 or GD 9 to 10 did not affect maternal ovarian and uterine circulation or ovarian hormone secretion rate as measured on GD 11 as compared with controls. However, exposure to *p*-

xylene for 48 h (GD 9 to 10) did result in a statistically significant decrease in the peripheral levels of progesterone and β-estradiol and significantly decreased fetal body weight (actual data not provided). It was proposed that the hepatic enzyme induction by *p*-xylene was responsible for increased metabolism of the sex hormones, which in turn was responsible for fetotoxicity. Ungváry and Donáth (1984) found that exposure of pregnant rats to *p*-xylene at approximately 350 ppm resulted in hyperinnervation or degeneration of noradrenergic nerves of reproductive organs (uterus, ovaries). They proposed that damage to the peripheral noradrenergic nerves can result in altered control of uterine and ovarian blood flow and steroid production, resulting in fetal toxicity.

4.3. Other Relevant Information

4.3.1. Interspecies Differences

Physiologically based pharmacokinetic (PBPK) modeling was done for rats and humans (see Appendix C). PBPK modeling allows a comparison of the internal dose in both species receiving identical external exposures. As shown in Figure 6C-9 in Appendix C, rats achieve higher blood *m*-xylene concentrations than humans at the same atmospheric xylene levels. This effect is primarily due to a higher blood-air partition coefficient (PB) in rats (46) compared with humans (26.4, 31.9, and 32.5) (Sato and Nakajima 1979; Gargas et al. 1989; Pierce et al. 1996). Other factors include the rats' higher respiratory (alveolar ventilation) rate and higher cardiovascular output and tissue blood flow rates.

The total interspecies factor includes the pharmacodynamic component as well. The available data indicate relatively little difference in interspecies sensitivity to xylene. Lethality data for mice and rats were nearly identical (Cameron et al. 1938; Bonnet et al. 1982). Death was preceded by narcosis and was likely the result of depression of the CNS resulting in respiratory arrest. Nonlethal effects in both humans and animals are similar and consist primarily of mucus irritation and CNS depression.

4.3.2. Intraspecies Differences

Available data point to a 2- to 3-fold difference in interindividual sensitivity to xylenes.

At sufficiently high concentrations, xylene acts as an anesthetic (Fang et al. 1996). Studies indicate that children, particularly infants, are more resistant than adults to the pharmacologic actions of various volatile anesthetics (Gregory et al. 1969; Stevens et al. 1975; Lerman et al. 1983; LeDez and Lerman 1987; Katoh and Ikeda 1992; Chan et al. 1996). The susceptibility of different age groups has been extensively studied in the medical literature where the concentrations of various anesthetic gases in the lung that produce "anesthesia" (lack of movement) have been measured (NRC 2002). Values are usually reported as the

minimum alveolar concentration (MAC) that produces lack of movement in 50% of persons exposed to that concentration. MACs for several anesthetic gases have been measured as a function of age. The results consistently show a pattern with maximal sensitivity (lowest MAC) in newborns, particularly prematures, pregnant women, and the elderly. The least sensitivity (highest MAC values) occurs in older infants, toddlers, and children as compared with adults. The total range of sensitivity is 2- to 3-fold. On the basis of this knowledge, it is not unreasonable to conclude that the same 2- to 3-fold difference in sensitivity exists among individuals exposed to xylenes.

4.3.3. Concentration-Exposure Duration Relationship

The two primary effects of xylene exposure are irritation and CNS effects. Irritation is considered a threshold effect and therefore should not vary over time. An AEGL value based on irritation is therefore not scaled across time but rather the same value is applied across all times.

The CNS effects of xylene are attributed to the low molecular weight and lipophilic nature, which allow the solvent to readily cross the blood-brain barrier (see Section 4.2). Distribution studies of xylene after inhalation have confirmed high concentrations of xylene in the brain and central and peripheral nervous system immediately after exposure, with substantial elimination often occurring by 1 h postexposure. The rapid onset and transient nature of CNS effects caused by xylene are likely due to direct interaction with molecular receptors in the CNS followed by the rapid elimination of xylene. Xylenes readily diffuse bidirectionally between the blood and brain, rapidly attaining and striving to maintain an equilibrium between the two compartments. The blood-brain partition coefficient is the ratio of the xylene concentrations in blood and brain under near-steady-state conditions. Thus, the arterial or venous blood concentration of xylene is a reliable index of the brain concentration and, in turn, the magnitude of the CNS depression that is due to the parent compound. Thus, the xylene-blood concentration is a key determinant of impaired CNS activity. Therefore, the venous xylene blood concentration (CV) after exposure would be expected to provide an internal dose measurement correlating with clinical signs. PBPK modeling (see Appendix C) was used to determine the internal dose (CV) producing poor coordination for the AEGL-2 and prostration for the AEGL-3 in rats. The human PBPK model of xylene was then run for each defined AEGL time period to determine the equivalent atmospheric exposure concentration producing the target CV.

4.3.4. PBPK Model

As discussed in Section 4.3.3, PBPK modeling was applied to derive the AEGL-2 and AEGL-3 values. The PBPK modeling process for xylenes is described in detail in Appendix C. Briefly, two research groups developed PBPK

models for *m*-xylene: one group developed a six-compartment model in rats and a seven-compartment model in humans; the other group developed a four-compartment model in rats and humans (Kaneko et al. 1991a,b, Tardif et al. 1993, 1997; Haddad et al. 1999; Kaneko et al. 2000). The basic model generated by Tardif et al. (1993, 1997) and Haddad et al. (1999) was chosen for the AEGL derivations because it was more data rich. The main difference among the models was in the physiologic parameters used. The rat model from Haddad et al. (1999) was chosen because it was the more recent, was more data rich, and had a better fit. The Haddad et al. (1999) model was optimized by using the Tardiff et al. (1993) gas uptake data (500, 1,000, 2,000, and 4,000 ppm). The acute lethality critical study (AEGL-3) is based on an exposure concentration (2,800 ppm) that lies within the range of concentrations used in the gas uptake study. The model was then visually reoptimized for *m*- and *p*-xylene with the available human data. Finally, the internal dose (CV) producing the toxicity end point of concern in rats was determined. The human PBPK model of xylene was then run for each defined AEGL time period to determine the equivalent atmospheric exposure concentration producing the target CV.

4.3.5. Comparison of the Toxicity of Individual Xylene Isomers

Because xylene exists as a mixture or as any of three individual isomers, the question arises as to whether there are differences in toxicity among the individual isomers and the mixture. PBPK model predictions indicate that the internal dose (CV) after exposure does not vary significantly among the individual isomers (see Figure 6C-10 in Appendix C).

Fang et al. (1996) determined the MAC (the concentration that produces anesthesia, or lack of movement, in 50% of those exposed) of the individual isomers in rats. The MACs of *o*-, *m*-, and *p*-xylene were 0.00118 ± 0.00009, 0.00139 ± 0.00010, and 00.00151 ± 0.0007 atmospheres, respectively, with a difference in MAC values of less than 30% among the isomers.

Only a limited number of studies were found in the open literature comparing the toxicity of the individual xylene isomers. Although differences did exist among the studies, no consistent, significant differences in the toxicologic potency of the xylene isomers after oral or inhalation exposure were identified (Ungváry et al. 1980; Moser et al. 1985; Molnár et al. 1986; Condie et al. 1988; Korsak et al. 1990).

5. DATA ANALYSIS AND PROPOSED AEGL-1

5.1. Human Data Relevant to AEGL-1

Exposure to mixed xylenes at 100, 200 or 400 ppm for 30 min resulted in (nonstatistically) increased complaints of eye irritation; no increased nose or throat irritation was noted and no changes in behavioral tests or respiratory

measurements were evident in controlled studies (Hastings et al. 1984). That mild degree of eye irritation is supported by observation that the number of eye blinks per minute was not affected by exposure. Exposure to *p*-xylene at 100 or 150 ppm for 7.5 h/day, 5 days/week resulted in mild eye irritation, most often in one male wearing contact lenses (irritation was noted on the first exposure day) (Hake et al.1981). No effects on performance tests were observed at these levels. Exposure to mixed xylenes at 110 ppm for 15 min resulted in intermittent, mild throat irritation in 1/6 individuals, while exposure to 230 ppm for 15 min resulted in eye irritation and mild dizziness in 1/7 individuals (Carpenter et al. 1975b).

A number of controlled human studies reported no adverse effects after exposure to xylenes. Exposure to *m*- or *p*-xylene at 100 or 200 ppm for 3 or 7 h failed to influence blood pressure, pulse rate, flicker value, or reaction time (Ogata et al. 1970). Olson et al. (1985) found exposure to *p*-xylene at 70 ppm for 4 h had no effect on choice reaction time, simple reaction time, short-term memory, heart rate, or subjective symptoms in exposed volunteers. No adverse effects on VEP, tapping speed, body sway, reaction time, or critical flicker fusion were measured in volunteers exposed to *m*-xylene at 200 ppm for 4 h (Savolainen et al. 1981; Seppalainen et al. 1983). Body sway, reaction time, and active or quiet sleep were not affected by exposure to 200 ppm for 5.5 h (Laine et al. 1993).

5.2. Animal Data Relevant to AEGL-1

No signs of toxicity were observed in dogs exposed to mixed xylenes at 530 ppm or in rats exposed to 580 ppm for 4 h, while lacrimation in dogs and poor coordination in rats were observed at 1,200 and 1,300 ppm, respectively (Carpenter et al. 1975b). In the study investigating conditioned flavor aversion, a concentration-related decrease in relative saccharin consumption was observed in all groups exposed to *p*-xylene for 4 h, with maximal aversion occurring in the 800- and 1,600-ppm groups (Bushnell and Peele 1988). The premise of the conditioned flavor aversion paradigm is combining exposure to a chemical with the introduction of something new, such as saccharine water. The animals then associate any negative effects they experience from exposure to the chemical with the consumption of the new food item and develop an aversion to the food item. Although it is a nonsensory effect, aversion represents an AEGL-1 effect.

5.3. Derivation of AEGL-1

The AEGL-1 is based on mild eye irritation in human subjects noted by Hastings et al. (1984) during a 30-min exposure to mixed xylenes at 400 ppm. The Hastings et al. (1984) results were considered most relevant because exposure was to mixed xylenes and represented a concentration at which an AEGL-1 effect was observed. An interspecies uncertainty factor was not applied because

the key study used human data. An intraspecies uncertainty factor of 3 was applied because slight eye irritation is caused by a direct effect of the chemical and the response is not expected to vary greatly among individuals. Irritation is considered a threshold effect, which should not vary over time; therefore, the AEGL-1 value was not scaled across time, but rather the same value is applied across all times. AEGL-1 values are presented in Table 6-12.

The 130-ppm value is supported by several other studies, including the *p*-xylene 150-ppm exposure resulting in eye irritation in a contact lens wearer (represents sensitive population; Hake et al. 1981); the 15-min exposure to mixed xylenes at 230 ppm resulting in mild eye irritation and dizziness in one individual; and the 3-h exposure to *m*- or *p*-xylene at 200 ppm (Ogata et al. 1970), the 4-h exposure to *m*-xylene at 200 ppm (Savolainen et al. 1981), and the 5.5-h exposure to *m*-xylene at 200 ppm (Laine et al. 1993). All these values represent acute NOAELs in adult humans.

6. DATA ANALYSIS AND PROPOSED AEGL-2

6.1. Human Data Relevant to AEGL-2

One of six or seven individuals noted dizziness during a 15-min exposure to mixed xylenes at 230 ppm (during the last 2 min of exposure) or 460 ppm (starting at the 6th minute and continuing to the end of exposure in the same individual), while a 15-min exposure to 690 ppm resulted in dizziness and lightheadedness in 4/6 individuals (Carpenter et al. 1975b). In the same study, a 15-min exposure resulted in eye irritation in 1/7, 4/6, and 4/6 individuals exposed to mixed xylenes at 230, 460, and 690 ppm, respectively.

6.2. Animal Data Relevant to AEGL-2

Exposure to mixed xylenes at 1,200 ppm for 4 h represents a threshold for lacrimation in dogs, while rats exposed to 1,300 ppm exhibited poor coordination (reversible) 2 h into a 4-h exposure (Carpenter et al. 1975b). The 4-h *m*-xylene EC_{50} for decreased rotarod performance in rats was 1,982 ppm (Korsak et al. 1993), and the 4-h minimum narcotic concentrations for the three xylene isomers in rats ranged from 1,940 to 2,180 ppm (Molnár et al. 1986). Exposure of rats to *p*-xylene at 1,600 ppm for 4 h resulted in hyperactivity, fine tremor, and unsteadiness (Bushnell 1989) and caused changes in the flash evoked potential suggestive of increased arousal (Dyer et al. 1988).

TABLE 6-12 AEGL-1 Values for Xylenes

10 min	30 min	1 h	4 h	8 h
130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)	130 ppm (560 mg/m^3)

After 30-min static exposures in mice, Moser et al. (1985) determined that the EC_{50} for decreased performance on the inverted screen test was 3,790 ppm for *m*-xylene, 3,640 ppm for *o*-xylene, and 2,676 ppm for *p*-xylene, while the EC_{50} for disruption of operant performance was 6,176 ppm for *m*-xylene, 5,179 ppm for *o*-xylene, and 5,611 ppm for *p*-xylene.

6.3. Derivation of AEGL-2

The AEGL-2 is based on the threshold for reversible equilibrium disturbances and the no-effect level for the impaired ability to escape. Poor coordination was observed in rats 2 h into a 4-h exposure to mixed xylenes at 1,300 ppm (Carpenter et al. 1975b). This concentration and end point are consistent with the preponderance of available data for 4-h exposures in rats: the EC_{50} for decreased rotarod performance was 1,982 ppm (Korsak et al. 1993); the minimum narcotic concentrations for *m*-, *o*-, and *p*-xylene ranged from 1,940 to 2,180 ppm (Molnár et al. 1986); and exposure to *p*-xylene at 1,600 ppm resulted in hyperactivity, fine tremor, and unsteadiness (Bushnell 1989) and caused changes in the flash evoked potential suggestive of increased arousal (Dyer et al. 1988). It is assumed that the CNS response observed after xylene exposure is directly related to the concentration of parent material reaching the brain and that CV values correlate with brain concentrations. Therefore, the CV of xylene after a 2-h exposure to xylene at 1,300 ppm is expected to provide an internal dose measurement correlating with the clinical sign of poor coordination. The internal dose (CV) producing impaired coordination in rats was determined with the PBPK model (see Appendix C). Then, the human PBPK model was run for each defined AEGL time period to determine the equivalent exposure concentration producing the target CV.

A total uncertainty factor of 3 was applied to the AEGL-2 and AEGL-3 dose metrics. An intraspecies uncertainty factor of 3 was applied for the pharmacokinetic and pharmacodynamic uncertainty because the MAC for volatile anesthetics should not vary by more than 2- to 3-fold among humans (NRC 2002). An interspecies uncertainty factor of 3 would usually be applied. PBPK modeling reduced the toxicokinetic component of the uncertainty factor to 1, but the pharmacodynamic component would normally be retained and assigned a 3 (although it appears that similar CNS effects occur in humans and animals, it is not known if they occur at the same tissue dose). A total uncertainty factor of 10, however, drives the AEGL-2 value for 8 h (180 ppm) to an exposure concentration that humans are known to tolerate with minimal or no adverse effects. Humans exposed to *p*-xylene at 150 ppm for 7.5 h did not exhibit any effects on performance tests and noted only mild eye irritation (Hake et al. 1981). Therefore, the interspecies uncertainty factor is reduced to 1, and a total uncertainty factor of 3 is applied to the AEGL-2 values (NRC 2002).

AEGL-2 values are presented in Table 6-13.

TABLE 6-13 AEGL-2 Values for Xylenes

10 min	30 min	1 h	4 h	8 h
2,500 ppm (11,000 mg/m^3)	1,300 ppm (5,600 mg/m^3)	920 ppm (4,000 mg/m^3)	500 ppm (2,200 mg/m^3)	400 ppm (1,700 mg/m^3)

The human data reported by Carpenter et al. (1975b) were not used for the AEGL-2 derivation as the exposure duration was brief (15 min) and it was not consistent with the preponderance of human data from other controlled human exposures. If one were to use the highest exposure concentration (690 ppm) that resulted in eye irritation and dizziness in 4/6 individuals, a threshold for equilibrium effects, and apply the intraspecies uncertainty factor of 3, one would obtain a value of 230 ppm. This concentration is supposed to represent a concentration at which exposed individuals could experience irreversible or other serious, long-lasting adverse health effects or have an impaired ability to escape. However, a number of studies demonstrated no adverse effects after exposure to *m*- or *p*-xylene at 100 or 200 ppm for 3 or 7 h (Ogata et al. 1970), to *m*-xylene at 200 ppm for 4 h (Savolainen et al. 1981), or to *m*-xylene at 200 ppm for 5.5 h (Laine et al. 1993). The Ogata et al. (1970) study found no effect on the ability to escape at 200 ppm for 3 or 7 h and thus supports the AEGL-2 value. However, it is not appropriate to use this study to derive the AEGL-2 value as 200 ppm is far below the threshold for CNS effects.

7. DATA ANALYSIS AND PROPOSED AEGL-3

7.1. Human Data Relevant to AEGL-3

Morley et al. (1970) reported the cases of three individuals exposed to xylene at approximately 10,000 ppm for about 18 h. One individual died, and the other two were found unconscious but experienced a full recovery.

7.2. Animal Data Relevant to AEGL-3

Two cats exposed to mixed xylenes at 9,500 ppm exhibited signs of CNS depression followed by death 2 h into the exposure (Carpenter et al. 1975b). In rats, 4-h LC_{50} values for mixed xylenes have been reported as 6,350 ppm (Hine and Zuidema 1970), 6,011 ppm (Carpenter et al. 1975b), and 11,000 ppm (Lundberg et al. 1986), and for *p*-xylene as 4,645 ppm (Harper et al. 1975). Six-hour LC_{50} values for the *m*-, *o*-, and *p*-isomers were 5,984, 4,330, and 4,591 ppm, respectively, in rats and 5,267, 4,595, and 3,907 ppm, respectively, in mice (Bonnet et al. 1979; 1982).

A no-effect level for death in rats after exposure to mixed xylenes for 4 h was 2,800 ppm (Carpenter et al. 1975b). Clinical signs observed during exposure to 2,800 ppm included prostration between 2 and 3.5 h into the exposure.

Recovery occurred within 1 h postexposure, but coordination remained poor until the following day. At the next lower concentration of 1,300 ppm, poor coordination was noted 2 h into the exposure, with coordination returning to normal after the exposure. Molnár et al. (1986) reported 4-h minimum narcotic concentrations of 2,100, 2,180, and 1,940 ppm for the *m*-, *o*-, and *p*-xylene isomers, respectively.

RD_{50} values in mice were 1,467 ppm for *o*-xylene (de Ceaurriz et al. 1981), 1,361 ppm for *m*-xylene (Korsak et al. 1993), and 2,440 ppm for mixed xylenes (Korsak et al. 1988). Korsak et al. (1988, 1993) did not use the recommended strain of mice.

7.3. Derivation of AEGL-3

The AEGL-3 derivation is based on reversible prostration and a no-observed-effect level (NOEL) for death in rats exposed to 2,800 ppm for 4 h (Carpenter et al. 1975b). Although coordination initially remained poor, it returned to normal the following day. This concentration represents a threshold for marked CNS depression, which could lead to death. As for the AEGL-2, it is assumed that the CNS effects observed after xylene exposure are directly related to the concentration of parent material reaching the brain. Therefore, PBPK modeling (see Appendix C) was again used to calculate the internal dose (CV) correlating with an exposure of rats to 2,800 ppm for 4 h, which produced prostration. The human PBPK model was then run for each defined AEGL time period to determine the equivalent exposure concentration producing the target CV.

A total uncertainty factor of 3 was applied to the AEGL-2 and -3 dose metrics. An intraspecies uncertainty factor of 3 was applied for the pharmacokinetic and pharmacodynamic uncertainty because the MAC for volatile anesthetics should not vary by more than 2- to 3-fold among humans (NRC 2002). An interspecies uncertainty factor of 3 would usually be applied. PBPK modeling reduced the toxicokinetic component of the uncertainty factor to 1, but the pharmacodynamic component would normally be retained and assigned a 3 (although it appears that similar CNS effects occur in humans and animals, it is not known if they occur at the same tissue dose). A total uncertainty factor of 10, however, drives the 4-h AEGL-3 value to 447 ppm, an exposure concentration that humans are known to tolerate with minimal or no adverse effects. Numerous human studies investigated the effects of exposure to *m*-xylene at 130 to 200 ppm for 4 to 6 h, with 20-min peaks of 400 ppm with or without exercise (Savolainen and Linnavuo 1979; Savolainen et al. 1984, 1985a,b; Seppalainen et al. 1989, 1991; Laine et al. 1993) and found no effect or only minimal CNS effects. Therefore, the interspecies uncertainty factor is reduced to 1, and a total uncertainty factor of 3 is applied to the AEGL-3 values (NRC 2002).

AEGL-3 values are presented in Table 6-14.

TABLE 6-14 AEGL-3 Values for Xylenes

10 min	30 min	1 h	4 h	8 h
7,200 ppm (31,000 mg/m^3)	3,600 ppm (16,000 mg/m^3)	2,500 ppm (11,000 mg/m^3)	1,300 ppm (5,600 mg/m^3)	1,000 ppm (4,300 mg/m^3)

8. SUMMARY OF PROPOSED AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for xylenes summarized in Table 6-15 apply to each of the individual xylene isomers or a mixture of xylene isomers. AEGL-2 and AEGL-3 values are greater than 10% of the lower explosive limit. As discussed in Section 4.3.3, no significant differences in the potency of the isomers after oral or inhalation exposure were identified and metabolism of each isomer proceeds along the same pathways.

A useful way to evaluate the AEGL values in the context of existing empirical data is presented in Figure 6-2. For this plot, the toxic response was placed in severity categories. The severity categories fit into definitions of the AEGL health effects: no effects, discomfort, disabling, some lethality (an experimental concentration at which some of the animals died and some did not), and lethal. The effects that place an experimental result in a particular category vary according to the spectrum of data available on a specific chemical and the effects from exposure to that chemical. The doses often span a number of orders of magnitude, especially when human data exist. Therefore, the concentration is on a logarithmic scale. Figure 6-2 plots the xylene AEGL values along with the existing acute human and animal toxicity data for xylene in terms of the categories assigned to them.

TABLE 6-15 Summary and Relationship of AEGL Values

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (Nondisabling)	130 ppm (560 mg/m^3)	130 (560 mg/m^3)	130 (560 mg/m^3)	130 (560 mg/m^3)	130 (560 mg/m^3)
AEGL-2 (Disabling)	2,500 ppm[a] (11,000 mg/m^3)	1,300 ppm[a] (5,600 mg/m^3)	920 ppm[a] (4,000 mg/m^3)	500 ppm (2,200 mg/m^3)	400 ppm (1,700 mg/m^3)
AEGL-3 (Lethal)	—[b]	3,600 ppm[a] (16,000 mg/m^3)	2,500 ppm[a] (11,000 mg/m^3)	1,300 ppm[a] (5,600 mg/m^3)	1,000 ppm[a] (4,300 mg/m^3)

[a]Concentrations are at or higher than 1/10th of the LEL for all forms of xylene (*o*-xylene LEL, 9,000 ppm; *m*- and *p*-xylene LEL, 11,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.
[b]10-min AEGL-3 = 7,200 ppm is ≥50% LEL. Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

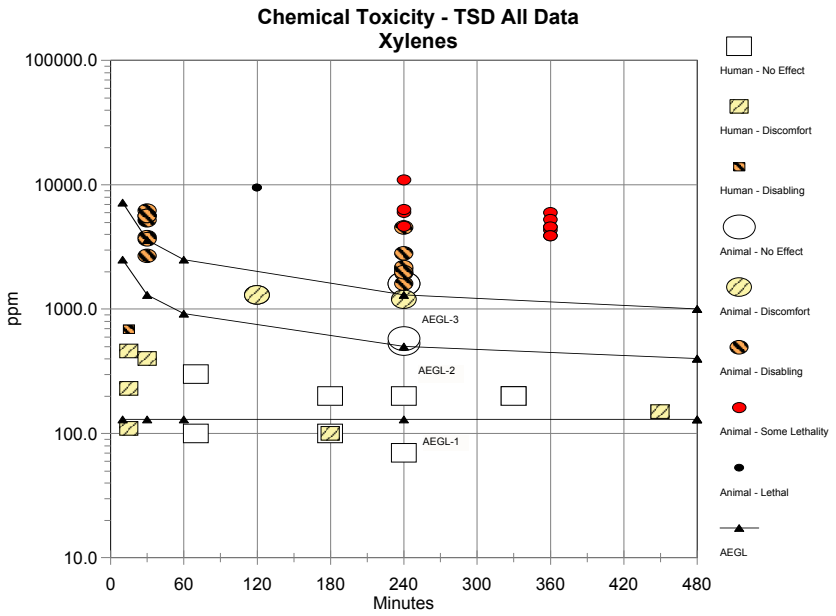


FIGURE 6-2 Category plot of human and animal toxicity data compared with AEGL values.

8.2. Comparisons with Other Standards

Standards and guidance levels for workplace and community exposures are listed in Table 6-16. The 130-ppm AEGL-1 is almost identical to the American Conference of Governmental Industrial Hygienists (ACGIH) and the National Institute for Occupational Safety and Health (NIOSH) 15-min short-term exposure limit (150 ppm), and it is close to the ACGIH, NIOSH, and Occupational Safety and Health Administration 8-h TWA (100 ppm). The 30-min AEGL-2 (1,300 ppm) and AEGL-3 (3,600 ppm) are higher than the 30-min concentration that is immediately dangerous to life or health (900 ppm).

8.3. Data Adequacy and Research Needs

Data appropriate for use in xylene AEGL derivations are robust. Numerous studies investigating controlled human exposures are available, but the effects noted are generally less serious than those defined by the AEGLs. Human lethality data are limited to a case report in which one of three individuals exposed to approximately 10,000 ppm for almost 19 h died (Morley et al. 1970). Animal data on nonlethal effects were available for dogs, cats, rats, and mice, although most of the data documenting CNS effects after acute exposure were

on rats. Lethality data were available for rats and mice and indicated little difference in sensitivity between these species.

Because of inadequate evidence, xylene is currently not classifiable as to carcinogenicity by IARC or the EPA.

TABLE 6-16 Extant Standards and Guidelines for Xylenes

	Exposure Duration						
Guideline	10 min	15 min	30 min	1 h	4 h	8 h	24 h
AEGL-1	130 ppm		130 ppm	130 ppm	130 ppm	130 ppm	
AEGL-2	2,500 ppm		1,300 ppm	920 ppm	5,00 ppm	400 ppm	
AEGL-3	7,200 ppm		3,600 ppm	2,500 ppm	1,300 ppm	1,000 ppm	
EEL (NRC)[a]				200 ppm			100 ppm
SMAC (NRC)[b]				100 ppm			100 ppm
IDLH (NIOSH)[c]			900 ppm				
TLV-TWA (ACGIH)[d]						100 ppm	
PEL-TWA (OSHA)[e]						100 ppm	
REL-TWA (NIOSH)[f]						100 ppm	
TLV-STEL (ACGIH)[g]		150 ppm					
REL-STEL (NIOSH)[h]		150 ppm					
MAK (Germany)[i]						440 mg/m^3 100 ppm	
MAC (The Netherlands)[j]						210 mg/m^3 50 ppm	

[a]EEL (emergency exposure limit, National Research Council) (NRC 1984) is defined as a ceiling limit for an unpredictable single exposure, usually lasting 60 min or less, and never more than 24 h—an occurrence expected to be rare in the lifetime of any person. It reflects an acceptance of the statistical likelihood of the occurrence of a nonincapacitating reversible effect in an exposed population. It is designed to avoid any substantial decrements in performance during emergencies and might contain no uncertainty factor. The use of uncertainty factors depends on the compound in question and on the type of effect it produces.

[b]SMAC (spacecraft maximum allowable concentration, National Research Council) (Garcia 1996) provides guidance on chemical exposures during normal operations of spacecraft as well as emergency situations. The 1-h SMAC is a concentration of airborne substance that will not compromise the performance of specific tasks by astronauts during emergency conditions or cause serious or permanent toxic effects. Such exposure may cause reversible effects, such as skin or eye irritation, but they are not expected to impair judgment or interfere with proper responses to emergencies.

[c]IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1996, 2005) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms or any irreversible health effects.
[d]TLV-TWA (Threshold Limit Value–time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2003) is the time-weighted average concentration for a normal 8-h workday and a 40-h workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.
[e]PEL-TWA (permissible exposure limit–time-weighted average, Occupational Health and Safety Administration) (29CFR Part 1910.1000 [1996]) is analogous to the ACGIH TLV-TWA but is for exposures of no more than 10 h/day, 40 h/week.
[f]REL-TWA (recommended exposure limit–time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2005) is analogous to the ACGIH TLV-TWA.
[g]TLV-STEL (Threshold Limit Value–short-term exposure limit, American Conference of Governmental Industrial Hygienists) (ACGIH 2003) is defined as a 15-min TWA exposure that should not be exceeded at any time during the workday even if the 8-h TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 min and should not occur more than four times per day. There should be at least 60 min between successive exposures in this range.
[h]REL-STEL (recommended exposure limit–short-term exposure limit, National Institute for Occupational Safety and Health) (NIOSH 2005) is a 15-min TWA exposure that should not be exceeded at any time during a workday.
[i]MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] (DFG 2002) is analogous to the ACGIH TLV-TWA.
[j]MAC (maximaal aanvaarde concentratie [maximal accepted concentration], Ministerie van Sociale Zaken en Werkgelegenheid (MSZW 2004) is analogous to the ACGIH TLV-TWA.

9. REFERENCES

Abu Al Ragheb, S., A.S. Salhab, and S.S. Amr. 1986. Suicide by xylene ingestion: A case report and review of literature. Am. J. Forensic Med. Pathol. 7(4):327-329.

ACGIH (American Conference of Governmental Industrial Hygienists). 1991. Xylene (*o-, m-,* and *p*-isomers). Pp. 1732-1740 in Documentation of the Threshold Limit Values and Biological Exposure Indices, 6th Ed. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 2003. Xylene (*o-, m-,* and *p*-isomers). P. 72 in TLVs and BEIs. Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices, 6th Ed. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

Anderson, B.E., E. Zeiger, M.D. Shelby, M.A. Resnick, D.K. Gulati, J.L. Ivett, and K.S. Loveday. 1990. Chromosome aberration and sister chromatid exchange test results with 42 chemicals. Environ. Mol. Mutagen. 16(Suppl. 18):55-137.

Andersson, K., K. Fuxe, O.G. Nilsen, R. Toftgard, P. Eneroth, and J.A. Gustafsson. 1981. Production of discrete changes in dopamine and noradrenaline levels and turnover in various parts of the rat brain following exposure to xylene, *ortho-, meta-,* and *para*-xylene, and ethylbenzene. Toxicol. Appl. Pharmacol. 60(3):535-548.

Anttila, A., R. Riala, E. Pukkala, M. Sallmén, S. Hernberg, and K. Hemminki. 1995. Occupational Exposure to Solvents and Cancer Incidence [in Finnish]. Finnish Institute of Occupational Health, Helsinki, Finland (as cited in Lynge et al. 1997).

Arp, E.W., Jr., P.H. Wolf, and H. Chekoway. 1983. Lypmphocytic leukemia and exposures to benzene and other solvents in the rubber industry. J. Occup. Med. 25(8):598-602.

Arthur, L.J., and D.A. Curnock. 1982. Xylene-induced epilepsy following innocent glue sniffing. Br. Med. J. 284(6331):1787.

Astrand, I. 1982. Work load and uptake of solvents in tissues of man. Pp. 141-152 in Advances in Modern Environmental Toxicology, Vol. 2, M.A. Mehlman, ed. Princeton, NJ: Princeton Scientific Publishers.

Astrand, I., J. Engström, and P. Övrum. 1978. Exposure to xylene and ethylbenzene. I. Uptake, distribution, and elimination in man. Scand. J. Work Environ. Health 4(3):185-194.

ATSDR (Agency for Toxic Substances and Disease Registry). 2007. Toxicological Profile for Xylene (Update). U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. August 2007 [online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp71.pdf [accessed June 9, 2010]

Bergman, K. 1983. Application and results of whole-body autoradiography in distribution studies of organic solvents. Crit. Rev. Toxicol. 12(1):59-118.

Bio/dynamics Inc. 1983. Parental and Fetal Reproduction Toxicity Study in Rats with Mixed Xylene. Document No. FYI-AX-0983-0209. Prepared for U.S. Environmental Protection Agency, by Bio/dynamics Inc., East Millstone, NJ.

Bliss, C.I. 1938. The determination of the dosage mortality curve from small numbers. Quart. J. Pharm. Pharmacol. 2:192-216.

Bonnet, P., G. Raoult, and D. Gradiski. 1979. Lethal concentration of 50 main aromatic hydrocarbons [in French]. Arch. Mal. Prof. 40(8-9):805-810.

Bonnet, P., Y. Morele, G. Raoult, D. Zissu, and D. Gradiski. 1982. Determination of the median lethal concentration of the main aromatic hydrocarbons in the rat [in French]. Arch. Mal. Prof. 43:261-265.

Bos, R.P., R.M. Brouns, R. van Doorn, J.L. Theuws, and P.T. Henderson. 1981. Nonmutagenicity of toulene*, o-, m-,* and *p*-xylene, *o*-methylbenzylalcohol and o-methylbenzylsufate in the Ames assay. Mutat. Res. 88(3):273-279.

Bray, H.G., B.G. Humphris, and W.V. Thorpe. 1949. Metabolism of derivatives of toluene: *o-, m-* and *p*-xylenes. Biochem. J. 45(2):241-244.

Budavari, S., M.J. O'Neil, A. Smith, P.E. Heckelman and J.F. Kinneary, eds. 1996. Propylene oxide. P. 1722-1723 in The Merck Index: An Encyclopedia of Chemicals, Drug, and Biologicals, 12th Ed. Whitehouse Station, NJ: Merck.

Bushnell, P.J. 1989. Behavioral effects of acute *p*-xylene inhalation in rats: Autoshaping, motor activity, and reversal learning. Neurotoxicol. Teratol. 10(6):569-577.

Bushnell, P.J., and D.B. Peele. 1988. Conditioned flavor aversion induced by inhaled *p*-xylene in rats. Neurotoxicol. Teratol. 10(3):273-277.

Cameron, C.R., J.L.H. Paterson, G.S.W. de Saram, and J.C. Thomas. 1938. The toxicity of some methyl derivatives of benzene with special reference to pseudocumene and heavy coal tar naphtha. J. Pathol. Bacteriol. 46(1):95-107.

Carlsson, A. 1981. Distribution and elimination of ^{14}C-xylene in rat. Scand. J. Work Environ. Health 7(1):51-55.

Carpenter, C.P., E.R. Kinkead, D.L. Geary Jr., L.J. Sullivan, and J.M. King. 1975a. Petroleum hydrocarbon toxicity studies. I. Methodology. Toxicol. Appl. Pharmacol. 32(2):246-262.

Carpenter, C.P., E.R. Kinkead, D.L. Geary Jr., L.J. Sullivan, and J.M. King. 1975b. Petroleum hydrocarbon toxicity studies. V. Animal and human response to vapors of mixed xylene. Toxicol. Appl. Pharmacol. 33(3):543-558.

Chan, M.T., P. Mainland, and T. Gin. 1996. Minimum alveolar concentration of halothane and enflurane are decreased in early pregnancy. Anesthesiology 85(4):782-786.

Condie, L.W., J.R. Hill, and J.F. Borzelleca. 1988. Oral toxicology studies with xylene isomers and mixed xylene. Drug Chem. Toxicol. 11(4):329-354.

de Ceaurriz, J.C., J.C. Micillino, P. Bonnet, and J.P. Guenier. 1981. Sensory irritation caused by various industrial airborne chemicals. Toxicol. Lett. 9(2):137-143.

de Gandarias, J.M., E. Echevarría, J. Irazusta, J. Gil, and L. Casis. 1993. Brain aminopeptidase activity after subacute xylene exposure. Neurotoxicol. Teratol. 15(1):51-53.

de Gandarias, J.M., E. Echevarría, E. Casis, L. Martínez-Millán, and L. Casis. 1995. Effects of acute xylene exposure on the enkephalinergic neuromodulatory system in rats. Ind. Health 33(1):1-6.

DFG (Deutsche Forschungsgemeinschaft). 2002. List of MAK and BAT Values 2002. Maximum Concentrations and Biological Tolerance Values at the Workplace Report No. 38. Weinheim, Federal Republic of Germany: Wiley VCH.

Donner, M., J. Maki-Paakkanen, H. Norppa, M. Sorsa, and H. Vainio. 1980. Genetic toxicology of xylenes. Mutat. Res. 74(3):171-172.

Drew, R.T., and J.R. Fouts. 1974. The lack of effects of pretreatment with phenobarbital and chlorpromazine on the acute toxicity of benzene in rats. Toxicol. Appl. Pharmacol. 27(1): 183-193.

Dudek, B., K. Gralewicz, M. Jakubowski, P. Kostrzewski, and J. Sokal. 1990. Neurobehavioral effects of experimental exposure to toluene, xylene and their mixture. Pol. J. Occup. Med. 3(1):109-116.

Dyer, R.S., M.S. Bercegeay, and L.M. Mayo. 1988. Acute exposures to xylene and toluene alter visual information processing. Neurotoxicol. Teratol. 10(2):147-153.

Engstrom, J., and V. Riihimaki. 1979. Distribution of *m*-xylene to subcutaneous adipose tissue in short-term experimental human exposure. Scand. J. Work Environ. Health 5(2):126-134.

Engstrom, J., V. Riihimaki, and A. Laine. 1984. Urinary disposition of ethylbenzene and *m*-xylene in man following separate and combined exposure. Int. Arch. Occup. Environ. Health 54(4):355-363.

EPA (U.S. Environmental Protection Agency). 2003. Xylenes (CASRN 1330-20-7). Integrated Risk Information System, U.S. Environmental Protection Agency [online]. Available: http://www.epa.gov/ncea/iris/subst/0270.htm [accessed June 8, 2010].

Fang, Z., J. Sonner, M.J. Laster, P. Ionescu, L. Kandel, D.D. Koblin, E.I. Eger, and M.J. Halsey. 1996. Anesthetic and convulsant properties of aromatic compounds and cycloalkanes: Implications for mechanisms of narcosis. Anesth. Analg. 83(5):1097-1104.

Fishbein, L. 1988. Xylenes: Uses, occurrence and exposure. Pp. 109-120 in Environmental Carcinogens: Methods of Analysis and Exposure Measurement, Vol. 10. Benzene and Alkylated Benzenes, L. Fishbein, and I.K. O'Neill, eds. IARC Scientific Publications 85. Lyon, France: World Health Organization.

Florin, I., L. Rutberg, M. Curvall, and C.R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 15(3):219-232.

Gamberale, F., G. Annwall, and M. Hultengren. 1978. Exposure to xylene and ethylbenzene. III. Effects on central nervous functions. Scand. J. Work Environ. Health 4(3):204-211.

Garcia, H.D. 1996. Xylene. Pp. 321-344 in Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 3. Washington, DC: National Academy Press.

Gargas, M.L., R.J. Burgess, D.E. Voisard, G.H. Cason, and M.E. Andersen. 1989. Partition coefficients of low molecular weight volatile chemicals in various liquids and tissues. Toxicol. Appl. Pharmacol. 98(1):87-99.

GENETOX (Genetic Toxicology Data Bank). 1992. Xylene (CASRN 1330-20-7). GENETOX, Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?GENETOX [accessed July, 2004].

Gérin, M., J. Siemiatycki, M. Désy, and D. Krewski. 1998. Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene: Results of a case-control study in Montreal. Am. J. Ind. Med. 34(2):144-156.

Gerner-Smidt, P., and U. Friedrich. 1978. The mutagenic effect of benzene, toluene, and xylene studied by the SCE technique. Mutat. Res. 58(2-3):313-316.

Ghantous, H., and B.R. Danielsson. 1986. Placental transfer and distribution of toluene, xylene and benzene, and their metabolites during gestation in mice. Biol. Res. Pregnancy Perinatol. 7(3):98-105.

Ghantous, H., L. Dencker, J. Gabreilsson, B.R. Danielsson, and K. Bergman. 1990. Accumulation and turnover of metabolites of toluene and xylene in nasal mucosa and olfactory bulb in the mouse. Pharmacol. Toxicol. 66(2):87-92.

Ghosh, T.K., R.L. Copeland, Jr., R.N. Parui, S. Mookherjee, and S.N. Pradhan. 1987. Effect of xylene inhalation on fixed-ratio responding in rats. Pharmacol. Biochem. Behav. 27(4): 653-657.

Goldie, I. 1960. Can xylene (xylol) provoke convulsive seizures? Ind. Med. Surg. 29:33-35.

Gregory, G.A., E.I. Eger II, and E.S. Munson. 1969. The relationship between age and halomethane requirements in man. Anesthesiology 30(5):488-491.

Gusev, I.S. 1965. Reflective effects of microconcentrations of benzene, toluene, xylene and their comparative assessment [in Russian]. Gyg. Sanit. 30(12):331-336.

Haddad, S., R. Tardif, G. Charest-Tardif, and K. Krishnan. 1999. Physiological modeling of the toxicokinetic interactions in a quaternary mixture of aromatic hydrocarbons. Toxicol. Appl. Pharmacol. 161(3):249-257.

Haglund, U., I. Lundberg, and L. Zech. 1980. Chromosome aberrations and sister chromatid exchanges in Swedish paint industry workers. Scand. J. Work Environ. Health 6(4):291-298.

Hake, C.L., R.D. Stewart, A. Wu, S.A. Graff, H.V. Forster, W.H. Keeler, A.J. Lebrun, P.E. Newton, and R.J. Soto. 1981. *p*-Xylene: Development of a Biological Standard for the Industrial Worker by Breath Analysis. PB82-152844. Prepared for National Institute for Occupational Safety and Health, Cincinnati, OH, by the Medical College of Wisconsin, Milwaukee, WI.

Harper, C., R.T. Drew, and J.R. Fouts. 1975. Benzene and *p*-xylene: A comparison of inhalation toxicities and *in vitro* hydroxylations. Pp. 302-311 in Biological Reactive Intermediates: Formation, Toxicity, and Inactivation, Proceedings of an International Conference, July 26-27, 1975, Turku, Finland, J. Jollow, ed. New York, NY: Plenum Press.

Hass, U., and B.M. Jakobsen. 1993. Prenatal toxicity of xylene inhalation in the rat: A teratogenicity and postnatal study. Pharmacol. Toxicol. 73(1):20-23.

Hass, U., S.P. Lund, L. Simonsen, and A.S. Fries. 1995. Effects of prenatal exposure to xylene on postnatal development and behavior in rats. Neurotoxicol. Teratol. 17(3):341-349.

Hass, U., S.P. Lund, and L. Simonsen. 1997. Long-lasting neurobehavioral effects of prenatal exposure to xylene in rats. Neurotoxicology 18(2):547-551.

Hastings, L., G.P. Cooper, and W. Burg. 1984. Human sensory response to selected petroleum hydrocarbons. Pp. 255-270 in Advances in Modern Environmental Toxicology, Vol. VI. Applied Toxicology of Petroleum Hydrocarbons, H.N. MacFarland, ed. Princeton, NJ: Princeton Scientific Publishers.

Hine, C.H., and H.H. Zuidema. 1970. The toxicological properties of hydrocarbon solvents. IMS Ind. Med. Surg. 39(5):215-220.

Hipolito, R.N. 1980. Xylene poisoning in laboratory workers: Case reports and discussion. Lab. Med. 11(9):593-595.

Holmberg, P.C., and M. Nurminen. 1980. Congenital defect of the central nervous system and occupational factors during pregnancy. A case-referent study. Am. J. Ind. Med. 1(2):167-176.

Honma, T., A. Sudo, M. Miyagawa, M. Sato, and H. Hasegawa. 1983. Significant changes in the amounts of neurotransmitter and related substances in rat brain induced by subacute exposure to low levels of toluene and xylene. Ind. Health 21(3):143-151.

Hudák, A., and G. Ungváry. 1978. Embryotoxic effects of benzene and its methyl derivatives: Toluene, xylene. Toxicology 11(1):55-63.

IARC (International Agency for Research on Cancer). 1999. Xylenes. Pp. 1189-1208 in Re-Evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 71. Lyon: IARC Press [online]. Available: http://monographs.iarc.fr/ENG/Monogr?aphs/vol71/volume71.pdf [accessed May 24, 2010].

Imbriani, M., S. Ghittori, G. Pezzagno, and E. Capodaglio. 1987. Urinary elimination of xylene in experimental and occupational exposure [in Italian]. Med. Lav. 78(3):239-249.

Inoue, O., K. Seiji, T. Kawai, T. Watanabe, C. Jin, S.X. Cai, Z. Chen, Q.S. Qu, T. Zhang, and M. Ikeda. 1993. Excretion of methlyhippuric acids in urine of workers exposed to a xylene mixture: Comparison among three xylene isomers and toluene. Int. Arch. Occup. Environ. Health 64(7):533-539.

Kaneko, T., K. Endoh, and A. Sato. 1991a. Biological monitoring of exposure to organic solvent vapors: I. Simulation studies using a physiological pharmacokinetic model for *m*-xylene. Yamanashi Med. J. 6:127-135.

Kaneko, T., K. Endoh, and A. Sato. 1991b. Biological monitoring of exposure to organic solvent vapors: II. Simulation studies using a physiological pharmacokinetic model for *m*-xylene. Yamanashi Med. J. 6:137-149.

Kaneko, T., J. Horiuchi, and A. Sato. 2000. Development of a physiologically based pharmacokinetic model of organic solvent in rats. Pharmacol. Res. 42(5):465-470.

Katoh, T., and K. Ikeda. 1992. Minimum alveolar concentration of seroflurane in children. Br. J. Anaesth. 68(2):139-141.

Kawai, T., K. Mizunuma, T. Yasugi, S. Horiguchi, Y. Uchida, O. Iwami, H. Iguchi, and M. Ikeda. 1991. Urinary methylhippuric acid isomer levels after occupational exposure to a xylene mixture. Arch. Occup. Environ. Health 63(1):69-75.

Kawai, T., T. Yasugi, K. Mizunuma, S. Horiguchi, H. Iguchi, Y. Uchida, O. Iwami, and M. Ikeda. 1992. Comparative evaluation of urinalysis and blood analysis as means of detecting exposure to organic solvents at low concentrations. Int. Arch. Occup. Environ. Health 64(4):223-234.

Klaucke, D.N., M. Johansen, and R.L. Vogt. 1982. An outbreak of xylene intoxication in a hospital. Am. J. Ind. Med. 3(2):173-178.

Korsak, Z., J.A. Sokal, A. Dedyk, T. Tomas, and R. Jedrychowski. 1988. Toxic effects of combined exposure to toluene and xylene in animals. I. Acute inhalation exposure. Pol. J. Occup. Med. 1(1):45-50.

Korsak, Z., J.A. Sokal, T. Wasiela, and R. Swiercz. 1990. Toxic effects of acute exposure to particular xylene isomers in animals. Pol. J. Occup. Med. 3(2):221-226.

Korsak, Z., R. Swiercz, and R. Jedrychowski. 1993. Effects of acute combined exposure to n-butyl alcohol and *m*-xylene. Pol. J. Occup. Med. Environ. Health 6(1):35-41.

Kucera, J. 1968. Exposure to fat solvents: A possible cause of sacral agenesis in man. J. Pediatr. 72(6):857-859.

Kükner, A., L. Canpolat, E. Ozan, A. Gökçimen, S. Ozan, and M. Doğrul. 1997-1998. The effect of xylene inhalation on the rat liver. Acta Physiol. Hung. 85(3):231-241.

Kumarathasan, P., R. Otson, and I. Chu. 1997. Measurement of the distribution of *m*-xylene in rat tissues by head space gas chromatography. Arh. Hig. Rada. Toksikol. 48(4):373-382.

Laine, A., K. Savolainen, V. Riihimaki, E. Matikainen, T. Salmi, and J. Juntunen. 1993. Acute effects of *m*-xylene inhalation on body sway, reaction times, and sleep in man. Int. Arch. Occup. Environ. Health 65(3):179-188.

Lazarew, N. 1929. On the toxicity of various hydrocarbon vapors [in German]. Arch. Exp. Pathol. Pharmacol 143:223-233.

LeDez, K.M., and J. Lerman. 1987. The minimum alveolar concentration (MAC) of isoflurane in preterm neonates. Anesthesiology 67(3):301-307.

Lerman, J., S. Robinson, M.M. Willis, and G.A. Gregory. 1983. Anesthetic requirements for halothane in young children 0-1 months and 1-6 months of age. Anesthesiology 59(5):421-424.

Litton Bionetics. 1978a. Teratology Study in Rats - Xylene. Final report. EPA/OTS Public Files, Document 878210347. Fiche No. OTS0231. Litton Bionetic, Kensington, MD.

Litton Bionetics. 1978b. Mutagenicity Evaluation of Xylene. EPA/OTS Public Files, Document 878210347. Litton Bionetics, Kensington, MD.

Lundberg, I., and J. Sollenberg. 1986. Correlation of xylene exposure and methyl hippuric acid excretion in urine among paint industry workers. Scand. J. Work Environ. Health 12(2): 149-153.

Lundberg, I., M. Ekdahl, T. Kronevi, V. Lidums, and S. Lundberg. 1986. Relative hepatotoxicity of some industrial solvents after intraperitoneal injection or inhalation exposure in rats. Environ. Res. 40(2):411-420.

Lynge, E., A. Anttila, and K. Hemminki. 1997. Organic solvents and cancer. Cancer Causes Control 8(3):406-419.

Maltoni, C., B. Conti, and G. Cotti. 1983. Benzene: A multipotential carcinogen. Results of long-term bioassays performed at the Bologna Institute of Oncology. Am. J. Ind. Med. 4(5): 589-630.

Maltoni, C., B. Conti, G. Cotti, and F. Belpoggi. 1985. Experimental studies on benzene carcinogenicity at the Bologna Institute of Oncology: Current results and ongoing research. Am. J. Ind. Med. 7(5-6):415-446.

McCarroll, N.E., C.E. Piper, and B.H. Keech. 1981. An E. coli microsuspension assay for the detection of DNA damage induced by direct-acting and promutagens. Environ. Mutagen. 3(4):429-444.

Miller, M.J., and J.W. Edwards. 1999. Possible preferential metabolism of xylene isomers following occupational exposure to mixed xylenes. Arch. Occup. Environ. Health 72(2): 89-97.

Mirkova, E., C. Zaikov, G. Antov, A. Mikhailova, L. Khinkova, and I. Benchev. 1983. Prenatal toxicity of xylene. J. Hyg. Epidemiol. Microbiol. Immunol. 27(3):337-343.

Mohtashamipur, E., K. Norpoth, U. Woelke, and P. Huber. 1985. Effects of ethylbenzene, toluene, and xylene on the induction of micronuclei in bone marrow polychromatic erythrocytes of mice. Arch. Toxicol. 58(2):106-109.

Molnár, J., K.A. Paksy, and M. Náray. 1986. Changes in the rat's motor behavior during 4-hr inhalation exposure to prenarcotic concentrations of benzene and its derivatives. Acta Physiol. Hung. 67(3):349-354.

Morley, R., D.W. Eccleston, C.P. Douglas, W.E. Greville, D.J. Scott, and J. Anderson. 1970. Xylene poisoning: A report on one fatal case and two cases of recovery after prolonged unconsciousness. Br. Med. J. 3(5720):442-443.

Moser, V.C., E.M. Coggeshall, and R.L. Balster. 1985. Effects of xylene isomers on operant responding and motor performance in mice. Toxicol. Appl. Pharmacol. 80(2):293-298.

MSZW (Ministerie van Sociale Zaken en Werkgelegenheid). 2004. Nationale MAC-lijst 2004: Xyleen (*o-,m- enp*-isomeren). Den Haag: SDU Uitgevers [online]. Available: http://www.lasrook.net/lasrookNL/maclijst2004.htm [accessed May 7, 2010].

Nelson, K.W., J.F. Ege Jr., M. Ross, L.E. Woodman, and L. Silverman. 1943. Sensory response to certain industrial solvent vapors. J. Ind. Hyg. Toxicol. 25(7):282-285.

NIOSH (National Institute for Occupational Safety and Health). 1996. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLH): NIOSH Chemical Listing and Documentation of Revised IDLH Values (as of 3/1/95)-Xylene (*o-, m-, p*-isomers). U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. August 1996 [online]. Available: http://www.cdc.gov/niosh/idlh/95476.html [accessed June 4, 2010].

NIOSH (National Institute for Occupational Safety and Health). 2005. NIOSH Pocket Guide to Chemical Hazards. NIOSH 2005-149. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati, OH. September 2005 [online]. Available: http://www.cdc.gov/niosh/npg/npgsyn-x.html [accessed June 4, 2010].

Norström, A., B. Andersson, L. Aringer, J.O. Levin, A. Löf, P. Näslund, and M. Wallèn. 1988. Determination of specific mercapturic acids in human urine after experimental exposure to toluene or *o*-xylene. Pp. 232-234 in Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention, H. Bartsch, K. Hemminki, and I.K. O'Neill, eds. IARC Scientific Publications No. 89. Lyon, France: IARC Press.

NRC (National Research Council). 1984. Xylene. Pp. 113-123 in Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 2. Washington, DC: National Academy Press.

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Washington, DC: National Academy Press.

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NRC (National Research Council). 2002. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 2. Washington, DC: The National Academies Press.

NTP (National Toxicology Program). 1986. NTP Technical Report on the Toxicology and Carcinogenesis of Xylene (mixed) (60% *m*-Xylene, 13.6% *p*-Xylene, 17.0% Ethylbenzene, and 9.1% *o*-Xylene) (CAS No. 1330-20-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP Technical Report 327. NIH 87-2583. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program, Research Triangle Park, NC.

OECD (Organisation for Economic Co-operation and Development). 2003. Chemical Screening Information Dataset (SIDS) for High Volume Chemicals. UNEP Chemicals, Geneva, Switzerland. May 2003.

Ogata, M., K. Tomokuni, and Y. Takatsuka. 1970. Urinary excretion of hippuric acid and *m*- or *p*-methylhippuric acid in the urine of persons exposed to vapours of toluene and *m*- or *p*-xylene as a test of exposure. Br. J. Ind. Med. 27(1):43-50.

Ogata, M., Y. Yamasaki, T. Meguro, R. Sugihara, and Y. Shimada. 1979. Quantitation of urinary *o*-xylene metabolites of rats and human beings by high-performance liquid chromatography. Ind. Health 17(2):123-125.

Ogata, M., Y. Yamazaki, R. Sugihara, Y. Shimada, and T. Meguro. 1980. Quantitation of urinary *o*-xylene metabolites of rats and human beings by high-performance liquid chromatography. Int. Arch. Occup. Environ. Health 46(2):127-139.

Olson, B.A., F. Gamberale, and A. Iregren. 1985. Coexposure to toluene and *p*-xylene in man: Central nervous functions. Br. J. Ind. Med. 42(2):117-122.

Padilla, S.S., and D.P. Lyerly. 1989. Effects of *p*-xylene inhalation on axonal transport in the rat retinal ganglion cells. Toxicol. Appl. Pharmacol. 101(3):390-398.

Pap, M., and C. Varga. 1987. Sister-chromatid exchanges in peripheral lymphocytes of workers occupationally exposed to xylenes. Mutat. Res. 187(4):223-225.

Patel, J.M., C. Harper, B.N. Gupta, and R.T. Drew. 1979. Changes in serum enzymes after inhalation exposure of *p*-xylene. Bull. Environ. Contam. Toxicol. 21(1-2):17-24.

Pierce, C.H., R.L. Dills, G.W. Silvey, and D.A. Kalman. 1996. Partition coefficients between blood or adipose tissue and air for aromatic solvents. Scan. J. Work Environ. Health 22(2): 112-118.

Recchia, G., L. Perbellini, G.F. Prati, P. Dean, and G. Ancona. 1985. Coma caused by probably accidental ingestion of xylene: Treatment with hemoperfusion using activated charcoal [in Italian]. Med. Lav. 76(1):67-73.

Richer, C.L., S. Chakrabarti, M. Senécal-Quevillon, M.A. Duhr, X.X. Zhang, and R. Tardif. 1993. Cytogenic effects of low-level exposure to toluene, xylene, and their mixture on human blood lymphocytes. Int. Arch. Occup. Environ. Health 64(8):581-585.

Riihimaki, V., and K. Savolainen. 1980. Human exposure to *m*-xylene. Kinetics and acute effects on the central nervous system. Ann. Occup. Hyg. 23(4):411-422.

Riihimaki, V., P. Pfäffli, K. Savolainen, and K. Pekari. 1979. Kinetics of *m*-xylene in man: General features of absorption, distribution, biotransformation and excretion in repetitive inhalation exposure. Scand. J. Work Environ. Health 5(3):217-231.

Rosen, M.B., K.M. Crofton, and N. Chernoff. 1986. Postnatal evaluation of prenatal exposure to *p*-xylene in the rat. Toxicol. Lett. 34(2-3):223-229.

Rosengren, L.E., P. Kjellstrand, A. Aurell, and K.G. Haglid. 1986. Irreversible effects of xylene on the brain after long term exposure: A quantitative study of DNA and the glial cell marker proteins S-100 and GFA. NeuroToxicology 7(3):121-135.

Ruth, J.H. 1986. Odor thresholds and irritation levels of several chemical substances: A review. Am. Ind. Hyg. Assoc. J. 47(3):A142-A151.

Sato, A., and T. Nakajima. 1979. Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. Br. J. Ind. Med. 36(3):231-234.

Savolainen, K., and M. Linnavuo. 1979. Effects of *m*-xylene on human equilibrium measured with a quantitative method. Acta Pharmacol. Toxicol. 44(4):315-318.

Savolainen, K., and V. Riihimaki. 1981. An early sign of xylene effect on human equilibrium. Acta Pharmacol. Toxicol. 48(3):279-283.

Savolainen, H., P. Pfäffli, M. Helojoki, and M. Tengén. 1979a. Neurochemical and behavioral effects of long-term intermittent inhalation of xylene vapour and simultaneous ethanol intake. Acta Pharmacol. Toxicol. 44(3):200-207.

Savolainen, K., V. Riihimaki, and M. Linnoila. 1979b. Effects of short-term xylene exposure on psychophysiological functions in man. Int. Arch. Occup. Environ. Health 44(4):201-211.

Savolainen, K., V. Riihimaki, A.M. Seppalainen, and M. Linnoila. 1980. Effects of short-term *m*-xylene exposure and physical exercise on the central nervous system. Int. Arch. Occup. Environ. Health 45(2):105-121.

Savolainen, K., V. Riihimaki, A. Laine, and J. Kekoni. 1981. Short-term exposure of human subjects to *m*-xylene and 1,1,1-trichloroethane. Int. Arch. Occup. Environ. Health 49(1): 89-98.

Savolainen, K., J. Kekoni, V. Riihimaki, and A. Laine. 1984. Immediate effects of *m*-xylene on the human central nervous system. Arch. Toxicol. (Suppl. 7):412-417.

Savolainen, K., V. Riihimaki, R. Luukkonen, and O. Muona. 1985a. Changes in the sense of balance correlate with concentrations of *m*-xylene in venous blood. Br. J. Ind. Med. 42(11):765-769.

Savolainen, K., V. Riihimaki, O. Muona, J. Kekoni, R. Luukkonen, and A. Laine. 1985b. Conversely exposure-related effects between atmospheric *m*-xylene concentrations and human body sense of balance. Acta Pharmacol. Toxicol. 57(2):67-71.

Sedivec, V., and J. Flek. 1976. The absorption, metabolism, and excretion of xylenes in man. Int. Arch. Occup. Environ. Health 37(3):205-217.

Senczuk, W., and J. Orlowski. 1978. Absorption of *m*-xylene vapours through the respiratory track and excretion of *m*-methylhippuric acid in urine. Br. J. Ind. Med. 35(1):50-55.

Seppalainen, A.M., T. Salmi, K. Savolainen, and V. Riihimaki. 1983. Visual evoked potentials in short-term exposure of human subjects to *m*-xylene and1,1,1-trichloroethane. Pp. 349-352 in Application of Behavioral Pharmacology in Toxicology, G. Zbinden, ed. New York: Raven Press.

Seppalainen, A.M., A. Laine, T. Salmi, V. Riihimaki, and E. Verkkala. 1989. Changes induced by short-term xylene exposure in human evoked potentials. Int. Arch. Occup. Environ. Health 61(7):443-449.

Seppalainen, A.M., A. Laine, T. Salmi, E. Verkkala, V. Riihimaki, and R. Luukkonen. 1991. Electroencephalographic findings during experimental human exposure to *m*-xylene. Arch. Environ. Health 46(1):16-24.

Sevcik, P., A. Hep, and M. Peslova. 1992. Intravenous xylene poisoning. Intensive Care Med. 18(6):377-378.

Siemiatycki, J. 1991. Risk Factors for Cancer in the Workplace, 1st Ed. Boca Raton, FL: CRC Press.

Smyth, H.F., C.P. Carpenter, C.S. Weil, U.C. Pozzani, and J.A. Striegel. 1962. Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107.

Spirtas, R., P.A. Stewart, J.S. Lee, D.E. Marano, C.D. Forbes, D.J. Grauman, H.M. Pettigrew, A. Blair, R.N. Hoover, and J.L. Cohen. 1991. Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. Br. J. Ind. Med. 48(8):515-530.

Stevens, W.C., W.M. Dolan, R.T. Gibbons, A. White, E.I. Eger, R.D. Miller, R.H. deJong, and R.M. Elashoff. 1975. Minimum alveolar concentration (MAC) of isoflurane with and without nitrous oxide in patients of various ages. Anesthesiology 42(2):197-200.

Tahti, H. 1992. The neurotoxicity of organic solvents, studied with in vitro models. Altern. Lab. Anim. 20:290-296.

Tardif, R., J. Brodeur, and G.L. Plaa. 1989. Simultaneous high-performance liquid chromatographic analysis of hippuric acid and *ortho-, meta-,* and *para*-methylhippuric acids in urine. J. Anal. Toxicol. 13(6):313-316.

Tardif, R., S. Lapare, K. Krishnan, and J. Brodeur. 1993. Physiologically based modeling of the toxicokinetic interaction between toluene and *m*-xylene in the rat. Toxicol. Appl. Pharmacol. 120(2):266-273.

Tardif, R., G. Charest-Tardif, J. Brodeur, and K. Krishnan. 1997. Physiologically based pharmacokinetic modeling of a ternary mixture of alkyl benzenes in rats and humans. Toxicol. Appl. Pharmacol. 144(1):120-134.

Taskinen, H., A. Anttila, M.L. Lindbohm, M. Sallmén, and K. Hemminki. 1989. Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. Scand. J. Work Environ. Health 15(5):345-352.

Taskinen, H., P. Kyyrönen, K. Hemminki, M. Hoikkala, K. Lajunen, and M.L. Lindbohm. 1994. Laboratory work and pregnancy outcome. J. Occup. Med. 36(3):311-319.

Tátrai, E., and G. Ungváry. 1980. Changes induced by *o*-xylene inhalation in the rat liver. Acta Med. Acad. Sci. Hung. 37(2):211-216.

Tátrai, E., G. Ungváry, I.R. Cseh, S. Mányai, S. Szeberényi, J. Molnár, and V. Morvai. 1981. The effect of long-term inhalation of *o*-xylene on the liver. Pp. 293-300 in Industrial and Environmental Xenobiotics: Metabolism and Parmacokinetics of Organic Chemicals and Metals, Proceedings of International Conference, May 27-30, 1980, Prague, Czechoslovakia, I. Gut, M.Cikrt, and G.L. Plaa, eds. New York: Springer-Verlag.

Tegeris, J.S., and R.L. Balster. 1994. A comparison of the acute behavioral effects of alkylbenzenes using a functional observational battery in mice. Fundam. Appl. Toxicol. 22(2):240-250.

Ungváry, G. 1990. The effect of xylene exposure on the liver. Acta Morphol. Hung. 38(3-4):245-258.

Ungváry, G., and T. Donáth. 1984. Effect of benzene and its methyl-derivatives (toluene, *para*-xylene) on postganglionic noradrenergic nerves. Z. Mikrosk. Anat. Forsch. 98(5):755-763.

Ungváry, G., and E. Tátrai. 1985. On the embryotoxic effects of benzene and its alkyl derivatives in mice, rats and rabbits. Arch. Toxicol. (Suppl. 8):425-430.

Ungváry, G., E. Tátrai, A Hudák, G. Barcza, and M. Lõrincz. 1980. Studies on the embryotoxic effects of *ortho-, meta-* and *para*-xylene. Toxicology 18(1):61-74.

Ungváry, G., B. Varga, E. Horváth, E. Tátrai, and G. Folly. 1981. Study on the role of maternal sex steroid production and metabolism in the embryotoxicity of *para*-xylene. Toxicology 19(3):263-268.

Washington, W.J., R.C. Murthy, A. Doye, K. Eugene, D. Brown, and I. Bradley. 1983. Induction of morphologically abnormal sperm in rats exposed to *o*-xylene. Arch. Androl. 11(3):233-237.

Wilcosky, T.C., H. Checkoway, E.G. Marshall, and H.A. Tyroler. 1984. Cancer mortality and solvent exposures in the rubber industry. Am. Ind. Hyg. Assoc. J. 45(12):809-811.

Wimolwattanapun, S., T.K. Ghosh, S. Mookherjee, R.L. Copeland Jr., and S.N. Pradhan. 1987. Effect of inhalation of xylene on intracranial self-stimulation behavior in rat. Neuropharmacology 26(11):1629-1632.

Windham, G.C., D. Shusterman, S.H. Swan, L. Fenster, and B. Eskenazi. 1991. Exposure to organic solvents and adverse pregnancy outcome. Am. J. Ind. Med. 20(2):241-259.

APPENDIX A

DERIVATION OF AEGL VALUES FOR XYLENE

Derivation of AEGL-1 Values

Key study:	Hastings et al. 1984
Toxicity end point:	Eye irritation in human volunteers exposed to mixed xylenes at 400 ppm for 30 min
Scaling:	Because irritation is considered a threshold effect and should not vary over time, the AEGL-1 value is not scaled across time but rather the threshold value is applied to all times.
Uncertainty factors:	1 for interspecies variability 3 for intraspecies variability
Modifying factor:	Not applicable
10-min, 30-min, 1-h, 4-h, 8-h AEGL-1:	Concentration producing effect was applied to all times: 400 ppm/3 = 130 ppm

Derivation of AEGL-2 Values

Key study:	Carpenter et al. 1975b
Toxicity end point:	Rats exposed 2 h into a 4-h exposure to 1,300 ppm exhibited poor coordination
Scaling:	It is assumed that the CNS effects observed after xylene exposure are directly related to parent material reaching the brain. Therefore, PBPK modeling (see Appendix C) was used to calculate the internal dose (CV) correlating to exposure to 1,300 ppm for 2 h, which produced poor coordination in rats. A human PBPK model was then run for each defined AEGL time period to determine the equivalent exposure concentration producing the target CV.

Uncertainty factors:	3 for intraspecies variability 1 for interspecies variability A total uncertainty factor of 10 would have driven the AEGL-2 value for 8 h (180 ppm) to an exposure concentration that humans are known to tolerate with minimal or no adverse effects: humans exposed to *p*-xylene at 150 ppm for 7.5 h did not exhibit any effects on performance tests and noted only mild eye irritation (Hake et al. 1981). Therefore, the interspecies uncertainty factor is reduced to 1, and a total uncertainty factor of 3 is applied to the AEGL-2 and AEGL-3 values (NRC 2002).
Modifying factor:	Not applicable
10-min AEGL-2:	Application of PBPK model: 2,500 ppm
30-min AEGL-2:	Application of PBPK model: 1,300 ppm
1-h AEGL-2:	Application of PBPK model: 920 ppm
4-h AEGL-2:	Application of PBPK model: 500 ppm
8-h AEGL-2:	Application of PBPK model: 400 ppm

Derivation of AEGL-3 Values

Key study:	Carpenter et al. 1975b
Toxicity end point:	Reversible prostration and a no-effect level for mortality in rats exposed to 2,800 ppm for 4 h
Scaling:	It is assumed that the CNS effects observed after xylene exposure are directly related to parent material reaching the brain. Therefore, PBPK modeling (see Appendix C) was again used to calculate the internal dose (CV) correlating to exposure at 2,800 ppm for 4 h, which produced prostration in rats. A human PBPK model was then run for each defined AEGL time period to determine the equivalent exposure concentration producing the target CV.

Uncertainty factors:	3 for intraspecies variability 1 for interspecies variability A total uncertainty factor of 10 drives the 4-h AEGL-3 value to 447 ppm, an exposure concentration that humans are known to tolerate with minimal or no adverse effects. Numerous human studies investigated the effects of exposure to *m*-xylene at 130 to 200 ppm for 4 to 6 h, with 20-min peaks of 400 ppm with or without exercise (Savolainen and Linnavuo 1979; Savolainen et al. 1984, 1985a,b; Seppalainen et al. 1989, 1991; Laine et al. 1993) and found no effect or minimal CNS effects. Therefore, the interspecies uncertainty factor is reduced to 1, and a total uncertainty factor of 3 is applied to the AEGL-2 and AEGL-3 values (NRC 2002).
Modifying factor:	Not applicable
10-min AEGL-3:	Application of PBPK model: 7,200 ppm
30-min AEGL-3:	Application of PBPK model: 3,600 ppm
1-h AEGL-3:	Application of PBPK model: 2,500 ppm
4-h AEGL-3:	Application of PBPK model: 1,300 ppm
8-h AEGL-3:	Application of PBPK model: 1,000 ppm

APPENDIX B

ACUTE EXPOSURE GUIDELINE LEVELS FOR XYLENES

Derivation Summary for Xylenes

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
130 ppm	130 ppm	130 ppm	130 ppm	130 ppm

Key Reference:
Hastings, L., G.P. Cooper, and W. Burg. 1984. Human sensory response to selected petroleum hydrocarbons. Pp. 255-270 in Advances in Modern Environmental Toxicology, Vol. VI. Applied Toxicology of Petroleum Hydrocarbons, H.N. MacFarland, ed. Princeton, NJ: Princeton Scientific Publishers.

Test Species/Strain/Number: Volunteer human male

Exposure Route/Concentrations/Durations: Subjects were exposed by inhalation via an olfactometer delivery hood to mixed xylenes at 0, 100, 200, or 400 ppm for 30 min

Effects: Mild eye irritation reported by 56%, 60%, 70%, and 90% of subjects exposed to mixed xylenes at 0, 100, 200, and 400 ppm, respectively; no effects observed on behavioral test results

End Point/Concentration/Rationale: Mild eye irritation was noted by 90% of the subjects exposed to 400 ppm

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1 for human data used
Intraspecies: 3 because slight eye irritation is caused by a direct effect of the chemical and the response is not expected to vary greatly among individuals.

Modifying Factor: Not applied

Animal to Human Dosimetric Adjustment: Not applied, human data used

Time-Scaling: Irritation is considered a threshold effect and should not vary over time. The AEGL-1 value based on irritation is therefore not scaled across time, but rather the threshold value is applied to all times.

Data Adequacy: This study was acceptable but could have been improved had the number of volunteers been reported. However, the data are consistent with other human studies and represent a value consistent with exposure concentrations that might result in mild eye irritation.

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
2,500 ppm	1,300 ppm	920 ppm	500 ppm	400 ppm

Key Reference:
Carpenter, C.P., E.R. Kinkead, D.L. Geary Jr., L.J. Sullivan, and J.M. King. 1975b. Petroleum hydrocarbon toxicity studies. V. Animal and human response to vapors of mixed xylenes. Toxicol. Appl. Pharmacol. 33(3): 543-558.

Test Species/Strain/Number: 10 male albino rats (Harlan-Wistar strain) approximately 5 weeks old per group

Exposure Route/Concentrations/Durations: Rats were exposed by inhalation to mixed xylenes at 580, 1,300, 2,800, 4,000, or 9,000 ppm for 4 h

Effects:

Concentration	Mortality	Other Effects
580 ppm	0/10	None observed
1,300 ppm	0/10	Poor coordination after 2 h, returned to normal
2,800 ppm	0/10	Irritation; all rats prostrate between 2 and 3.5 h recovered within 1 h;coordination returned to normal next day
6,000 ppm	4/10	Rats prostrate within 30 min; all survivors prostrate but recovered promptly
9,900 ppm	10/10	None stated

End Point/Concentration/Rationale: The AEGL-2 is based on the no-effect level for impaired ability to escape. During a 4-h exposure to mixed xylenes at 1,300 ppm, rats developed poor coordination (slight coordination loss) after 2 h of exposure, returning to normal coordination postexposure. The point of departure of 1,300 ppm for 2 h therefore represents the threshold for reversible equilibrium disturbances and the no-effect level for impaired ability to escape. It is assumed that the CNS effects observed after xylene exposure are directly related to parent material reaching the brain and that CV values correlate with brain concentrations. Therefore, the CV of xylene after a 2-h exposure to xylene at 1,300 ppm would be expected to provide an internal dose measurement correlating with the clinical sign of poor coordination. By using PBPK modeling (see Appendix C), the internal dose (CV) producing poor coordination in rats was determined. Then, a human PBPK model was run for each defined AEGL time period to determine the equivalent exposure concentration producing the target CV.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Intraspecies: 3. An intraspecies uncertainty factor of 3 was applied for the pharmacokinetic and pharmacodynamic uncertainty because the MAC for volatile anesthetics should not vary by more than 2- to 3-fold among humans (NRC 2002).
Interspecies: 1. An interspecies uncertainty factor of 3 would usually be applied. PBPK modeling reduced the toxicokinetic component of the uncertainty factor to 1, but the

(Continued)

AEGL-2 VALUES Continued

10 min	30 min	1 h	4 h	8 h
2,500 ppm	1,300 ppm	920 ppm	500 ppm	400 ppm

pharmacodynamic component would normally be retained and assigned a 3 (although it appears that similar CNS effects occur in humans and animals, it is not known if they occur at the same tissue dose). A total uncertainty factor of 10, however, drives the AEGL-2 value for 8 h (180 ppm) to an exposure concentration that humans are known to tolerate with minimal or no adverse effects. Humans exposed to *p*-xylene at 150 ppm for 7.5 h did not exhibit any effects on performance tests and noted only mild eye irritation (Hake et al. 1981). Therefore, the interspecies uncertainty factor is reduced to 1, and a total uncertainty factor of 3 is applied to the AEGL-2 values (NRC 2002).

Modifying Factor: Not applied

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: PBPK modeling predicted human exposure concentrations correlating with a target CV at each defined AEGL time period.

Data Adequacy: This was a well-designed and conducted study. The data are supported by numerous other studies in rats as well as a study in dogs. The AEGL-2 values are protective.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
7,200 ppm	3,600 ppm	2,500 ppm	1,300 ppm	1,000 ppm

Key Reference:
Carpenter, C.P., E.R. Kinkead, D.L. Geary Jr., L.J. Sullivan, and J.M. King. 1975b. Petroleum hydrocarbon toxicity studies. V. Animal and human response to vapors of mixed xylenes. Toxicol. Appl. Pharmacol. 33(3):543-558.

Test Species/Strain/Number: 10 male albino rats (Harlan-Wistar strain) approximately 5 weeks old per group

Exposure Route/Concentrations/Durations: Rats were exposed by inhalation to mixed xylenes at 580, 1,300, 2,800, 4,000, or 9,000 ppm for 4 h

Effects:

Concentration	Mortality	Other Effects
580 ppm	0/10	None observed
1,300 ppm	0/10	Poor coordination after 2 h, returned to normal
2,800 ppm	0/10	Irritation; all rats prostrate between 2 and 3.5 h recovered within 1 h;coordination returned to normal next day
6,000 ppm	4/10	Rats prostrate within 30 min; all survivors prostrate but recovered promptly
9,900 ppm	10/10	None stated

(Continued)

AEGL-3 VALUES Continued

10 min	30 min	1 h	4 h	8 h
7,200 ppm	3,600 ppm	2,500 ppm	1,300 ppm	1,000 ppm

End Point/Concentration/Rationale: The AEGL-3 derivation is based on reversible prostration and a NOEL for death in rats exposed to 2,800 ppm for 4 h. Although coordination initially remained poor, it returned to normal the following day. This concentration represents a threshold for marked CNS depression, which could lead to death. As for the AEGL-2, it is assumed that the CNS effects observed after xylene exposure are directly related to the concentration of parent material reaching the brain. Therefore, PBPK modeling (see Appendix C) was again used to calculate the internal dose (CV) correlating with an exposure to 2,800 ppm for 4 h, which produced prostration in rats. The human PBPK model was then run for each defined AEGL time period to determine the equivalent exposure concentration producing the target CV.

Uncertainty Factors/Rationale:

Total uncertainty factor: 3

Intraspecies: 3. An intraspecies uncertainty factor of 3 was applied for the pharmacokinetic and pharmacodynamic uncertainty because the MAC for volatile anesthetics should not vary by more than 2- to 3-fold among humans (NRC 2002).

Interspecies: 3. An interspecies uncertainty factor of 3 would usually be applied. PBPK modeling reduced the toxicokinetic component of the uncertainty factor to 1, but the pharmacodynamic component would normally be retained and assigned a 3 (although it appears that similar CNS effects occur in humans and animals, it is not known if they occur at the same tissue dose). A total uncertainty factor of 10, however, drives the 4-h AEGL-3 value to 447 ppm, an exposure concentration that humans are known to tolerate with minimal or no adverse effects. Numerous human studies investigated the effects of exposure to *m*-xylene at 130 to 200 ppm for 4 to 6 h, with 20-min peaks of 400 ppm with or without exercise (Savolainen and Linnavuo 1979; Savolainen et al. 1984, 1985a,b; Seppalainen et al. 1989, 1991; Laine et al. 1993) and found no effect or minimal CNS effects. Therefore, the interspecies uncertainty factor is reduced to 1, and a total uncertainty factor of 3 is applied to the AEGL-3 values (NRC 2002).

Modifying Factor: Not applied

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: PBPK modeling predicted human exposure concentrations correlating with a target CV at each defined AEGL time period.

Data Adequacy: This was a well-conducted study. The AEGL-3 levels are supported by human data demonstrating that exposure to 690 ppm for 15 min resulted in lightheadedness and dizziness and a 30-min exposure to 700 ppm resulted in nausea, vomiting, dizziness, or vertigo.

APPENDIX C

PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING OF XYLENE

Summary

Two research groups developed PBPK models for xylene, and both groups modeled the single isomer *m*-xylene. Kaneko et al. (1991ab, 2000) developed a six-compartment model in rats and a seven-compartment model in humans. The other research group developed a four-compartment model in rats and humans (Tardif et al. 1993, 1997; Haddad et al. 1999). The basic model generated by Tardif et al. (1993, 1997) and Haddad et al. (1999) was chosen for the AEGL derivations because it was more data rich. The main difference among the models was in the physiologic parameters used. The model was coupled with additional human data from five publications for verification (see Table 6C-1). Next, the rat model was run to determine CV at the exposure concentration producing the defined AEGL end point. Then the human model was run for each time period to determine the equivalent exposure concentration producing the same CV. The application of PBPK modeling to the derivation of the xylene AEGL values was based on guidance in the PBPK modeling White Paper (Dennison et al. 2009). All PBPK modeling was performed in Berkeley Madonna, version 8.0.2a8, a recent beta version that includes scripting capabilities (Macey and Oster 2002). A glossary of PBPK modeling abbreviations is provided at the end of this appendix.

Rat Model

The basis of the model was a standard four-compartment model that included richly perfused tissue, slowly perfused tissue, fat, and liver (Figure 6C-1), with the rate of change in the concentration in each tissue described by the equation shown below (Ramsey and Andersen 1984):

$$V_i dC_i/dt = Q_i(C_a - CV_i) - RAM,$$

where

V_i = tissue volume (L),
Q_i = tissue perfusion rate (L/h),
C_a = concentration of solvent in the systemic arterial blood (mg/L),
CV_i = concentration of solvent in venous blood leaving tissue, i (mg/L),
RAM = rate of change in the amount metabolized,
RAM = AMS + AML,
$AMS = V_{max} \times C_{VL}/(K_m + C_{VL})$,

AML = KF × C_{VL}, and
KF = first-order rate constant for high-capacity low-affinity enzymes.

It was assumed that metabolism occurred exclusively in the liver. V_{max} was scaled to the body weight by using $V_{max}C \times BW^{0.75}$. The following data were used to develop the rat PBPK model:

Gas-uptake data from rats exposed at 500, 1,000, 2,000, or 4,000 ppm (Tardif et al. 1993).
CV in rats after a 4-h exposure to 100 or 200 ppm (Tardif et al. 1997).
CV in rats after a 4-h exposure to 50 ppm (Haddad et al. 1999).
Partition parameters from Gargas et al. (1989) (in vitro).
Standard parameters for tissue flows and volumes (see Table 6C-2).

TABLE 6C-1 CV in Humans Exposed to *m*-Xylene at 200 ppm

Time (h)	CV (μmol/L)	Reference
0.12	11.6[a]	Seppalainen et al. 1991
0.15	12.6[a]	Seppalainen et al. 1991
0.18	14.3[a]	Seppalainen et al. 1991
0.22	16.4 a	Seppalainen et al. 1991
0.25	16.6 ± 4.8	Laine et al. 1993
0.33	17.3 ± 5.5	Laine et al. 1993
	17.5	Savolainen et al. 1985
0.5	17.5	Savolainen et al. 1984
0.67	21.3 ± 5.4	Laine et al. 1993
1	23.9*	Seppalainen et al. 1991
1.17	24.9 ± 2.1 (6)	Savolainen et al. 1981
1.5	26	Savolainen et al. 1984
2	28.5 ± 5.2	Laine et al. 1993
	29	Savolainen et al. 1984
2.5	26.7 ± 3.4 (6)	Savolainen et al. 1981
	30	Savolainen et al. 1984
	30	Savolainen et al. 1985
3	31	Seppalainen et al. 1989
	31.4	Seppalainen et al. 1991
3.75	28.6 ± 3.5 (6)	Savolainen et al. 1981

[a]These values read from a graph using digiMatic software (Digimatic 2004).

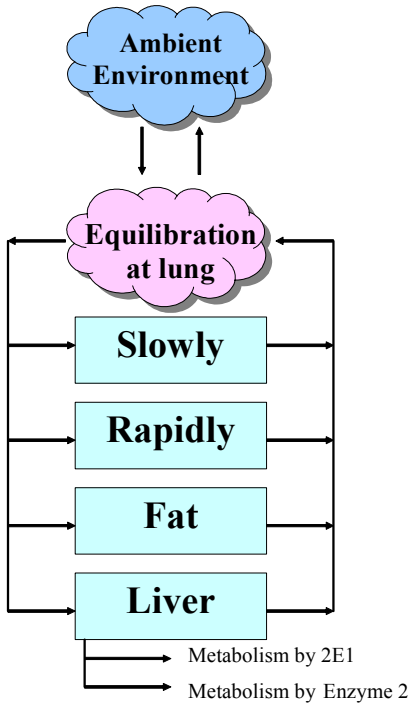


FIGURE 6C-1 Four-compartment rat model.

The rat model from Haddad et al. (1999) was chosen because it was more recent, was more data rich, and had a better fit. However, there was not a large difference among the models. The Haddad et al. (1999) model does have the limitation that it was created with data from Sprague-Dawley rats and had only postexposure data at xylene concentrations up to 200 ppm. In the more recent Haddad et al. (1999) model, slightly different parameters were used for tissue volumes and metabolism compared with the earlier model of Tardif et al. (1993). The 1999 model was run with the 1993 gas uptake data (500, 1,000, 2,000, and 4,000 ppm) (see Figure 6C-2). The results suggest that the 1993 and 1999 models are quite similar as the plot shown here is essentially the same as that in the 1993 paper. At the lower concentrations, the model would actually fit perfectly if the starting concentration were adjusted to the measured concentration. The acute lethality critical study (AEGL-3) is based on an exposure concentration (2,800 ppm) that lies within the range of concentrations used in the gas uptake study.

TABLE 6C-2 Summary of Parameter Values Used in Rat and Human PBPK Model

Variable	Rat[a]	Human[b]	
Body weight (kg) (BW)	0.1678	70	
Alveolar ventilation rate (L/h/kg) (QPC)[c]	15	14.9	
Cardiac output (L/h/kg) (QCC)[c]	15	12.4	
Fraction of body weight (kg/kg BW)			
Fraction fat tissue (VFC)	0.07	0.19[d]	
Fraction liver tissue (VLC)	0.04	0.026[d]	
Fraction rapidly perfused (VRC)	0.05	0.05[d]	
Fraction slowly perfused (VSC)	0.75	0.62[d]	
Fraction of cardiac output corresponding to each compartment ((L/h)/QC)			
Fraction blood flow to fat (QFC)	0.09	0.05	
Fraction to rapidly perfused (QRC)	0.51	0.42	
Fraction to liver (QLC)	0.25	0.32	
Fraction to slowly perfused (QSC)	0.15	0.21	
Partition coefficients			
Blood-air (PB)			
m-xylene	46[e]	32.5[e]; 26.4[f]; 31.9[g];	Average = 30.3
o-xylene	44.3[e]	34.9[e]; 31.1[f]; 35.2[g];	Average = 33.7
p-xylene	41.3[e]	44.7[e]; 37.6[f]; 39.0[g];	Average = 40.4

(Continued)

TABLE 6C-2 Continued

Variable	Rat[a]	Human[b]
Blood-fat (PFA)	1,859	1,859[a]
Slowly perfused-air (PSA)	41.9	41.9[a]
Rapidly perfused-air (PR)]	90.9	90.9[a]
Liver-air (PLA)	90.9	90.9[a]
Scaling coefficient (SF])	0.75	0.75
$V_{max}C$ (mg/h/kg)[g]	6.49	5.5
K_m (mg/L)	0.45	0.45[a]
KFC	0.1	0.1

[a]Haddad et al. 1999.
[b]Astrand 1983.
[c]QPC, QCC, and $V_{max}C$ were scaled to $BW^{0.75}$.
[d]Tardif et al. 1997.
[e]Gargas et al. 1989.
[f]Sato and Nakajima 1979.
[g]Pierce et al. 1996.

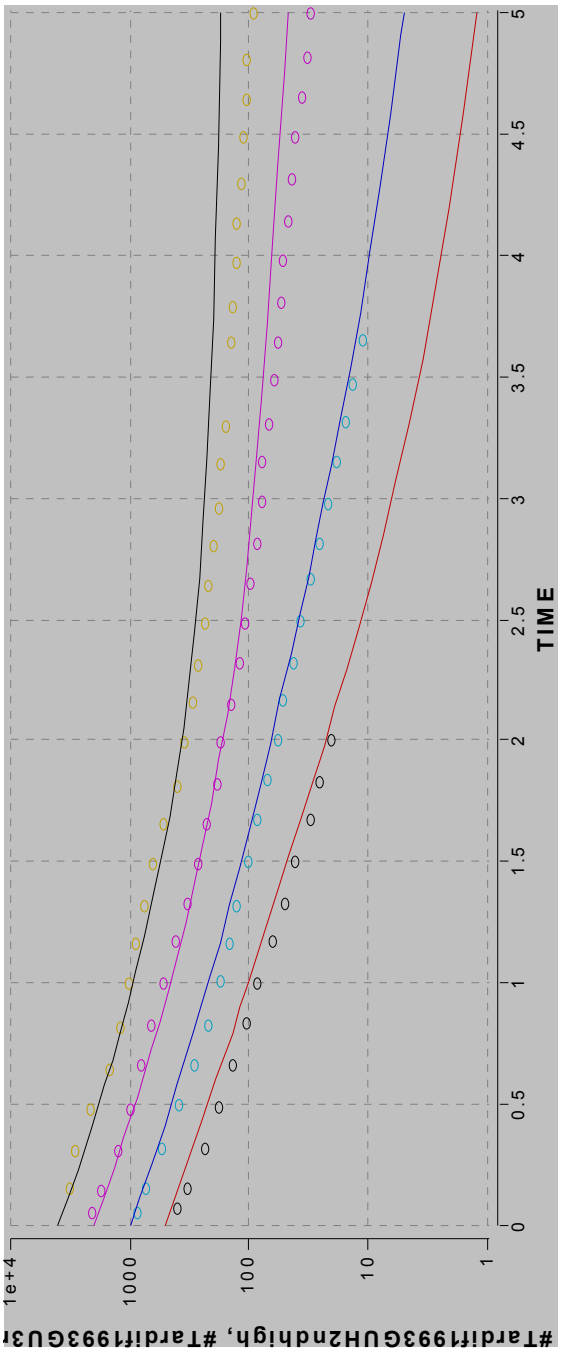


FIGURE 6C-2 The Haddad et al. (1999) model with the Tardif et al. (1993) gas uptake data (500, 1,000, 2,000, and 4,000 ppm).

Using the Haddad et al. (1999) model, the starting concentrations were optimized to reflect the measured concentrations of the first data points. At the high concentrations of interest for xylene, enzymatic saturation of the primary metabolic pathway may have occurred. Therefore, a second pathway of metabolism (lumped metabolism by all the CYPs other than CYP2E1) was added to account for high-capacity low-affinity pathways of metabolism, which would occur at the much higher exposure concentrations (Clewell et al. 2001). The metabolism by the second series of CYPs is given as

$$\text{Rate of metabolism (RAM)} = KF \times C_{VL},$$

where

C_{VL} = concentration of xylenes in the venous blood leaving the liver and
$KF = 0.1/BW^{0.3}$.

The second pathway of metabolism was added and KF (first-order rate constant for high-capacity low-affinity enzymes) was determined. Figure 6C-3 shows the results of optimizing the starting concentrations and adding the second pathway of metabolism. Adding the second metabolic pathway resulted in a very close correspondence between the model and the data.

After optimizing the Haddad model with the Tardif et al. (1993) data, the model was run again with the same parameters against the Haddad data (Figure 6C-4). A good fit is obtained overall, although the 200-ppm experimental data are slightly underpredicted. However, the concern is primarily with estimating CV in rats at very high concentrations (1,000 to 3,000 ppm). Figure 6C-4 shows what the model does without the second metabolic pathway (perfect fit) and with it. There is no real difference at 50 or 100 ppm, but the second line from the top is the new model at 200 ppm.

Application of the Model to Humans

The optimized rat model can now be used to develop a xylene PBPK model for humans. The model was visually reoptimized for *m*- and *p*-xylene with the available human data. Multiple papers were available in which human *m*-xylene CV values were measured during exposure to *m*-xylene at 200 ppm (Savolainen et al. 1981, 1984, 1985; Seppalainen et al. 1989, 1991; Laine et al. 1993) (see Table 6C-1). Postexposure human CV were also reported by Hake et al. (1981) after exposure to *p*-xylene at 20, 100, or 150 ppm for 1, 3, or 7 h and by Tardif et al. (1997) after exposure to *m*-xylene at 33 ppm for 7 h.

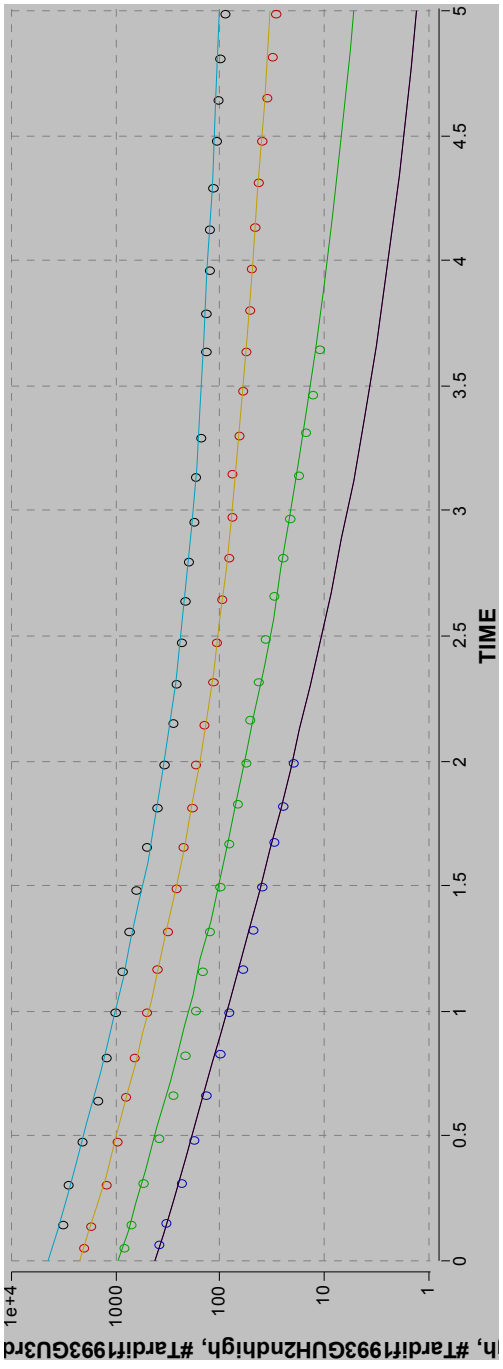


FIGURE 6C-3 The Haddad et al. (1999) model with the Tardif et al. (1993) gas uptake data (500, 1,000, 2,000, and 4,000 ppm), optimized for the starting concentration and inclusion of a second metabolism pathway.

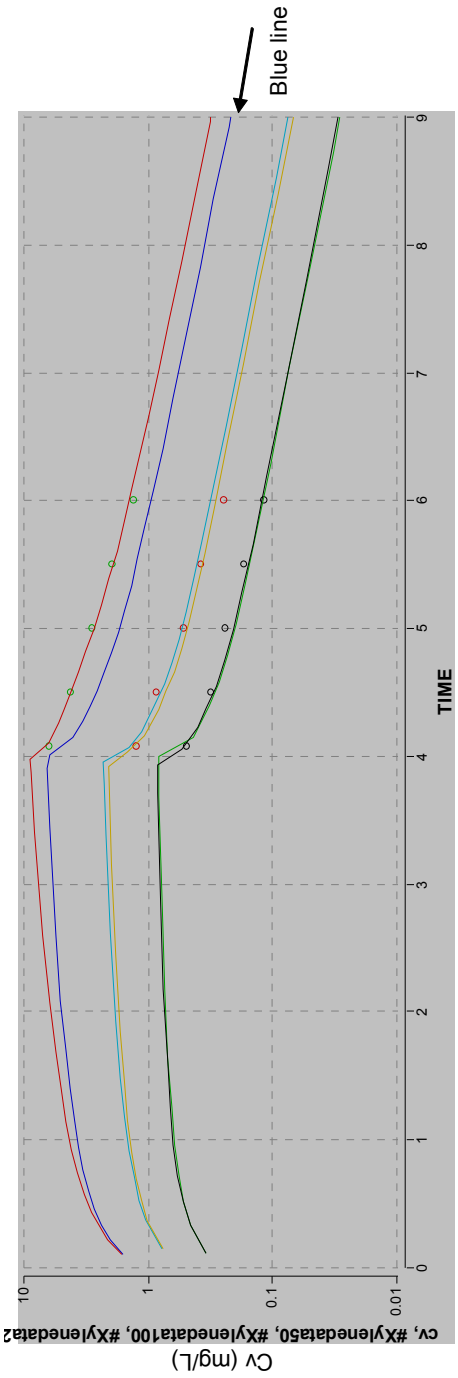
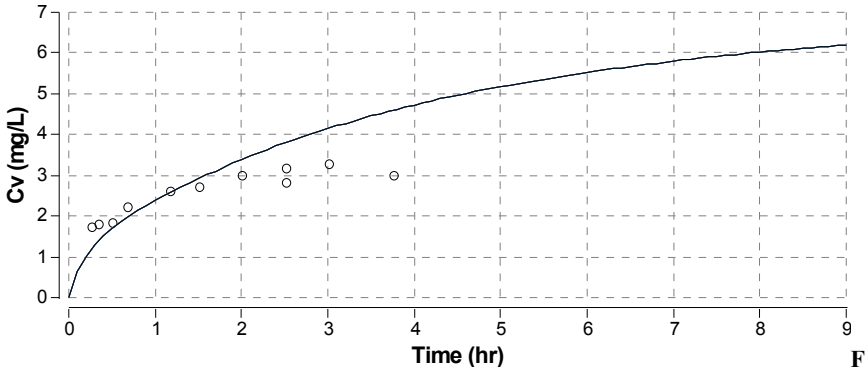


FIGURE 6C-4 Haddad et al. (1999) model after being optimized for the Tardif et al. (1993) gas uptake data.

Human anatomic parameters were generally taken from Astrand (1983) (see Table 6C-2). Kinetics were scaled from the rat model except for $V_{max}C$, which was reoptimized and reduced to 5.5. Without the adjustment, the model tended to underpredict most of the data. Values for QCC or QPC were not optimized because these values came from part of a physiologic parameter set (Astrand 1983). Several human blood-air partition coefficients (PB) for the xylene isomers were reported in the literature and are presented in Table 6C-2. The average PB for the respective xylene isomer was used for modeling data. Figures 6C-5 to 6C-8 show the reoptimized human model predictions for CV for *m*- or *p*-xylene compared with the measured human CV values.



IGURE 6C-5 Model predictions of CV (line; using human input parameters with PB of 30.3) compared with the actual measured human CV values during exposure to *m*-xylene at 200 ppm (open circles; combined data summarized in Table 6C-1).

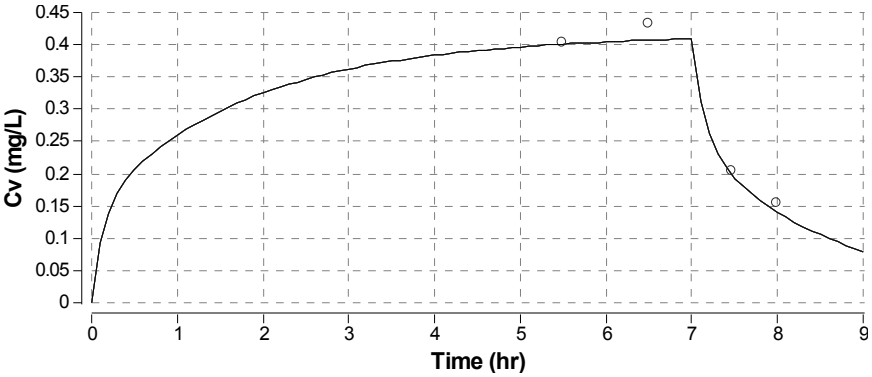


FIGURE 6C-6 Mmodel predictions of CV (line; using human input parameters with PB of 30.3) compared with the actual measured human CV values (open circles) during and after exposure to *m*-xylene at 33 ppm for 7 h (Tardif et al. 1997).

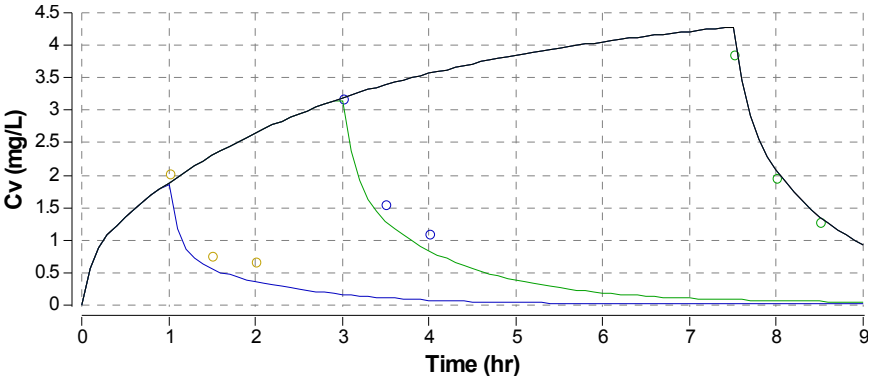


FIGURE 6C-7 Model predictions of CV (line; using male human input parameters with PB of 40.4) compared with the actual measured male human CV values (open circles) after exposure to *p*-xylene at 150 ppm for 1, 3, or 7.5 h (Hake et al. 1981).

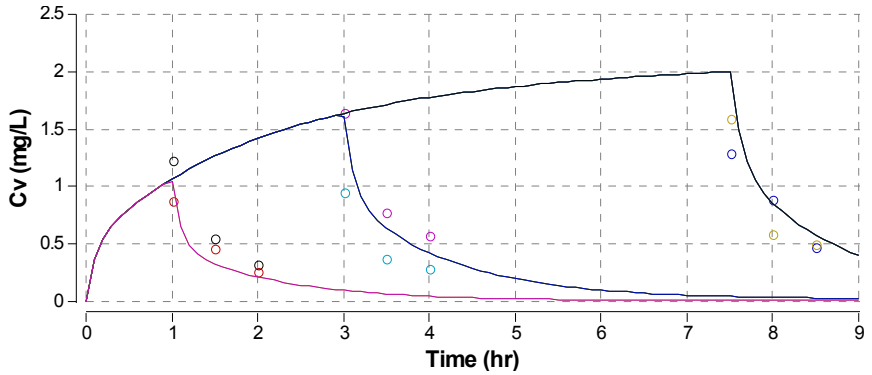


FIGURE 6C-8 Model predictions of CV (lines; using human female input parameters with PB of 40.4) compared with the actual measured human female CV values (open circles) after exposure to *p*-xylene at 100 ppm for 1, 3, or 7.5 h (Hake et al. 1981).

Comparison of Pharmacokinetics in Rats and Humans

Because the AEGL-2 and AEGL-3 key studies are based on rat data, extrapolation to humans is required. PBPK modeling allows a comparison of the internal dose that is received in both species receiving identical external exposures. As shown in Figure 6C-9, rats achieve higher blood *m*-xylene concentrations than humans. This is primarily due to a higher PB in rats (46) compared with humans (26 to 32 in humans). Figure 6C-9 plots CV for rats and humans using the validated models presented earlier at 200, 1,000, and 5,000 ppm.

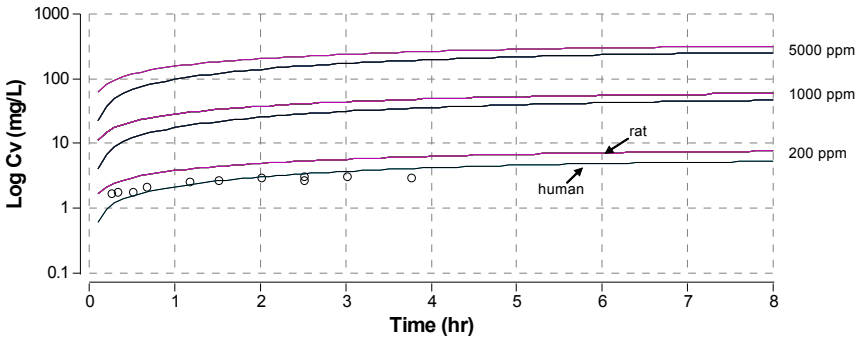


FIGURE 6C-9 Model predictions for CV in rats (top line of each pair of lines) and humans (bottom line of each pair of lines). Open circles are the actual measured human CV values for exposure to xylene at 200 ppm.

The y axis in Figure 6C-9 is on a logarithmic scale. By 8 h, steady state is still slowly increasing.

Application of Modeling to Derive AEGL Values

Because xylene can exist as a mixture or as any of three individual isomers, the question arises as to whether there are any differences in toxicity among the individual isomers and the mixture. No significant differences in the potency of the isomers after oral or inhalation exposure were identified and metabolism of each isomer proceeds via the same pathway. PBPK model predictions indicate that the internal dose (CV) after exposure does not vary significantly among the individual isomers (see Figure 6C-10).

The AEGL-2 and -3 values are based on a study in rats exposed to mixed xylenes for 4 h (Carpenter et al. 1975). The composition of the mixed xylenes used was provided as follows:

Component	Volume Percent
Nonaromatics	0.07
Toluene	0.14
Ethylbenzene	19.27
p-Xylene	7.84
m-Xylene	65.01
o-Xylene	7.63
C_9 + aromatics	0.04
Total	100.00

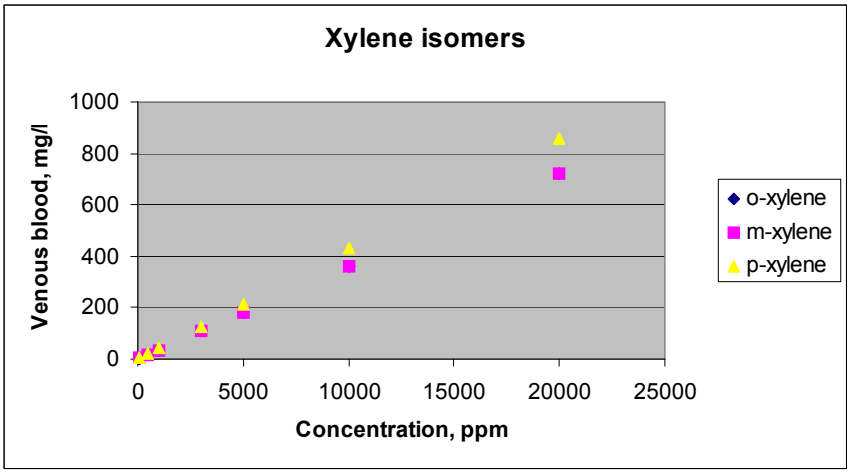


FIGURE 6C-10 The model predictions for CV in humans after exposure to the individual isomers (model parameters remain the same with the exception of PB values specific to the individual isomers; symbol for *m*-xylene is superimposed on symbol for *o*-xylene).

The amount of ethylbenzene is a typical amount seen in a xylene mixture. For the purpose of the modeling, it is known that ethylbenzene has the same spectrum of neurotoxic effects as xylenes, so assuming the exposure is to xylenes alone is reasonable. When considering only the amount of xylene isomers in the mixture and normalizing them to a total of 100%, 80% is the *m*-xylene isomer, while 10% is the *o*-xylene isomer and 10% is the *p*-xylene isomer. Therefore, the PB for *m*-xylene is used in the model.

The AEGL-2 derivation is based on poor coordination exhibited in rats 2 h into a 4-h exposure to mixed xylenes at 1,300 ppm (Carpenter et al. 1975). The rat PBPK model predicts that an exposure to xylenes at 1,300 ppm for 2 h would result in a CV of 48.9 mg/L. It is assumed that this internal dose of 48.9 mg/L is the dose resulting in the clinical sign of poor coordination. Therefore, it is assumed that the same internal dose of 48.9 mg/L would also result in adverse effects in humans. Using the human PBPK model, the model was run for each defined AEGL time point to determine the equivalent exposure concentration producing the same CV.

The AEGL-3 derivation is based on reversible prostration and a NOEL for death in rats exposed to 2,800 ppm for 4 h (Carpenter et al. 1975). The rat PBPK model predicts that an exposure to xylenes at 2,800 ppm for 4 h would result in a CV of 143.8 mg/L. Therefore, it is assumed that the same internal dose of 143.8 mg/L would also result in adverse effects in humans. Using the human PBPK model, the model was run for each defined AEGL time point to determine the equivalent exposure concentration producing the same CV.

Recommended AEGL Values

A total uncertainty factor of 3 was applied to the AEGL-2 and -3 dose metrics.

An intraspecies uncertainty factor of 3 was applied for the pharmacokinetic and pharmacodynamic uncertainty because the MAC for volatile anesthetics should not vary by more than 2- to 3-fold among humans (NRC 2002).

An interspecies uncertainty factor of 3 would usually be applied. PBPK modeling reduced the toxicokinetic component of the uncertainty factor to 1, but the pharmacodynamic component would normally be retained and assigned a 3 (although it appears that similar CNS effects occur in humans and animals, it is not known if they occur at the same tissue dose). A total uncertainty factor of 10, however, drives the 8-h AEGL-2 value to 180 ppm and the 4-h AEGL-3 value to 447 ppm. These are exposure concentrations that humans are known to tolerate with minimal or no adverse effects. With regard to the AEGL-2, humans exposed to *p*-xylene at 150 ppm for 7.5 h did not exhibit any effects on performance tests and noted only mild eye irritation (Hake et al. 1981). With regard to the AEGL-3, numerous human studies investigated the effects of exposure to *m*-xylene at 130 to 200 ppm for 4 to 6 h, with 20-min peaks of 400 ppm with or without exercise (Savolainen and Linnavuo 1979; Savolainen et al. 1984, 1985; Seppalainen et al. 1989, 1991; Laine et al. 1993) and found no effect or minimal CNS effects. Therefore, the interspecies uncertainty factor is reduced to 1, and a total uncertainty factor of 3 is applied to the AEGL-2 and AEGL-3 values (NRC 2002).

GLOSSARY OF PBPK MODEL TERMS

Most used in the presentation:

CV	venous blood concentration
PB	Blood-air partition coefficient

Physiologic Parameters

BW	Body weight (kg)
QPC	Alveolar ventilation rate (L/h/kg)
QCC	Cardiac output (L/h/kg)
VFC	Fraction fat tissue (kg/(kg/BW))
VLC	Fraction liver tissue (kg/(kg/BW))
VRC	Fraction rapidly perfused (kg/(kg/BW))
QFC	Fractional blood flow to fat ((L/h)/QC)
QLC	Fractional blood flow to liver ((L/h)/QC)
QRC	Fractional blood flow to rapidly perfused ((L/h)/QC)
SF	Scaling coefficient

Chemical-Specific Parameters

PLA =	Liver-air partition coefficient
PFA =	Fat-air partition coefficient
PSA =	Slowly perfused air partition coefficient
PRA =	Rapidly perfused air partition coefficient
PB =	Blood-air partition coefficient
PL = PLA/PB	Liver-blood partition coefficient
PF = PFA/PB	Fat-blood partition coefficient
PS = PSA/PB	Slowly perfused blood partition coefficient
PR = PRA/PB	Rapidly perfused blood partition coefficient
MW =	Molecular weight (g/mol)
$V_{max}C$ =	Maximum velocity of metabolism (mg/h/kg)
K_m =	Michaelis-Menten (mg/L)
KFC =	0.1
CONC =	Inhaled concentration (ppm)

Calculated Parameters

$QC = QCC \times BW^{SF}$	Cardiac output
$QP = QPC \times BW^{SF}$	Alveolar ventilation
$VS = VSC \times BW$	Volume slowly perfused tissue (L)
$VF = VFC \times BW$	Volume fat tissue (L)
$VL = VLC \times BW$	Volume liver (L)
$VR = VRC \times BW$	Volume rapidly perfused (L)
$QF = QFC \times QC$	Blood flow to fat (L/h)
$QL = QLC \times QC$	Blood flow to liver (L/h)
$QS = QC - QF - QL - QR$	Blood flow to non-fat tissue (L/h)
$QR = QRC \times QC$	Blood flow to rapidly perfused (L/h)
$CIX = CONC \times MW/24,450$	Exposure concentration (mg/L)
$V_{max} = V_{max}C \times BW^{SF}$	
$KF = KFC/BW^{0.3}$	First-order rate constant for high-capacity low-affinity enzymes

REFERENCES

Astrand, I. 1983. Effect of physical exercise on uptake, distribution and elimination of vapors in man. Pp. 107-130 in Modeling of Inhalation Exposures to Vapors: Uptake, Distribution, and Elimination, V. Fiserova-Bergerova, ed. Boca Raton, FL: CRC Press.

Carpenter, C.P., E.R. Kinkead, D.L. Geary Jr., L.J. Sullivan, and J.M. King. 1975. Petroleum hydrocarbon toxicity studies. V. Animal and human response to vapors of mixed xylene. Toxicol. Appl. Pharmacol. 33(3):543-558.

Clewell, H.J., P.R. Gentry, J.M. Gearhart, B.C. Allen, and M.E. Andersen. 2001. Comparison of cancer risk estimates for vinyl chloride using animal and human data with a PBPK model. Sci. Total Environ. 274(1-3):37-66.

Dennison, J.E., C.M. Troxel, and R. Benson. 2009. PBPK Modeling White Paper: Addressing the Use of PBPK Models to Support Derivation of Acute Exposure Guideline Levels. AEGL National Advisory Committee. September 1, 2009.

Digimatic. 2004. Digimatic, Version 2. FEBSoftware, Chesterfield, VA.

Gargas, M.L., R.J. Burgess, D.E. Voisard, G.H. Cason, and M.E. Anderson. 1989. Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Toxicol. Appl. Pharmacol. 98(1):87-99.

Haddad, S., R. Tardif, G. Charest-Tardif, and K. Krishnan. 1999. Physiological modeling of the toxicokinetic interactions in a quaternary mixture of aromatic hydrocarbons. Toxicol. Appl. Pharmacol. 161(3):249-257.

Hake, C.L., R.D. Stewart, A. Wu, S.A. Graff, H.V. Forster, W.H. Keeler, A.J. Lebrun, P.E. Newton, and R.J. Soto. 1981. *p*-Xylene: Development of a Biological Standard for the Industrial Worker by Breath Analysis. PB82-152844. Prepared for National Institute for Occupational Safety and Health, Cincinnati, OH, by the Medical College of Wisconsin, Milwaukee, WI.

Kaneko, T., K. Endoh, and A. Sato. 1991a. Biological monitoring of exposure to organic solvent vapors. I. Simulation studies using a physiological pharmacokinetic model for *m*-xylene. Yamanashi Med. J. 6:127-135.

Kaneko, T., K. Endoh, and A. Sato. 1991b. Biological monitoring of exposure to organic solvent vapors. II. Simulation studies using a physiological pharmacokinetic model for *m*-xylene. Yamanashi Med. J. 6:137-149.

Kaneko, T., J. Horiuchi, and A. Sato. 2000. Development of a physiologically based pharmacokinetic model of organic solvent in rats. Pharmacol. Res. 42(5):465-470.

Laine, A., K. Savolainen, V. Riihimaki, E. Matikainen, T. Salmi, and J. Juntunen. 1993. Acute effects of *m*-xylene inhalation on body sway, reaction times, and sleep in man. Int. Arch. Occup. Environ. Health 65(3):179-188.

Macey, R.I., and G.F. Oster. 2002. Berkeley Madonna. University of California, Berkley, CA [online]. Available: http://www.berkeleymadonna.com/ [accessed June 11, 2010]

NRC (National Research Council). 2002. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 2. Washington, DC: The National Academies Press.

Pierce, C.H., R.L. Dills, G.W. Silvey, and D.A. Kalman. 1996. Partition coefficients between blood or adipose tissue and air for aromatic solvents. Scan. J. Work Environ. Health 22(2):112-118.

Ramsey, J.C., and M.E. Andersen. 1984. A physiologically-based description of the inhalation pharmacokinetics of styrene in rats and humans. Toxicol. Appl. Pharmacol. 73(1):159-175.

Sato, A., and T. Nakajima. 1979. Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. Br. J. Ind. Med. 36(3):231-234.

Savolainen, K., and M. Linnavuo. 1979. Effects of *m*-xylene on human equilibrium measured with a quantitative method. Acta Pharmacol. Toxicol. 44(4):315-318.

Savolainen, K., V. Riihimaki, A. Laine, and J. Kekoni. 1981. Short-term exposure of human subjects to *m*-xylene and 1,1,1-trichloroethane. Int. Arch. Occup. Environ. Health 49(1):89-98.

Savolainen, K., J. Kekoni, V. Riihimaki, and A. Laine. 1984. Immediate effects of *m*-xylene on the human central nervous system. Arch. Toxicol. (Suppl. 7):412-417.

Savolainen, K., V. Riihimaki, O. Muona, J. Kekoni, R. Luukkonen, and A. Laine. 1985. Conversely exposure-related effects between atmospheric *m*-xylene concentrations and human body sense of balance. Acta Pharmacol. Toxicol. 57(2):67-71.

Seppalainen, A.M., Laine, A., Salmi, T., Riihimaki, V., and Verkkala, E. 1989. Changes induced by short-term xylene exposure in human evoked potentials. Int. Arch. Occup. Environ. Health. 61: 443-449.

Seppalainen, A.M., A. Laine, T. Salmi, E. Verkkala, V. Riihimaki, and R. Luukkonen. 1991. Electroencephalographic findings during experimental human exposure to *m*-xylene. Arch. Environ. Health 46(1):16-24.

Tardif, R., S. Lapare, K. Krishnan, and J. Brodeur. 1993. Physiologically based modeling of the toxicokinetic interaction between toluene and *m*-xylene in the rat. Toxicol. Appl. Pharmacol. 120(2):266-273.

Tardif, R., G. Charest-Tardif, J. Brodeur, and K. Krishnan. 1997. Physiologically based pharmacokinetic modeling of a ternary mixture of alkyl benzenes in rats and humans. Toxicol. Appl. Pharmacol. 144(1):120-134.