Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 17

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. W81K04-11-D-0017 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: 978-0-309-30476-4
International Standard Book Number-10: 0-309-30476-8

Additional copies of this report are available for sale from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 3343313; 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. C. D. Mote, Jr., 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. C. D. Mote, Jr., are chair and vice chair, respectively, of the National Research Council.

www.national-academies.org

Members

COMMITTEE ON ACUTE EXPOSURE GUIDELINE LEVELS

EDWARD C. BISHOP (*Chair*), HDR Engineering, Inc., Omaha, NE
DEEPAK K. BHALLA, Wayne State University, Detroit, MI
LUNG CHI CHEN, New York University, Tuxedo
KATHLEEN L. GABRIELSON, Johns Hopkins School of Medicine, Baltimore, MD
GUNNAR JOHANSON, Karolinska Institute, Stockholm, Sweden
MARGARET M. MACDONELL, Argonne National Laboratory, Argonne, IL
DAVID A. MACYS, U.S. Department of the Navy (retired), Oak Harbor, WA
MARIA T. MORANDI, University of Montana, Missoula
LEENA A. NYLANDER-FRENCH, University of North Carolina, Chapel Hill, NC
FRANZ OESCH, University of Mainz (retired), Mainz, Germany
NU-MAY RUBY REED, California Environmental Protection Agency (retired), Davis
GEORGE C. RODGERS, University of Louisville, Louisville, KY
ROBERT SNYDER, Rutgers University, Piscataway, NJ
KENNETH R. STILL, Portland State University, Portland, OR

Staff

SUSAN N.J. MARTEL, Senior Program Officer
TAMARA DAWSON, Program Associate
MIRSADA KARALIC-LONCAREVIC, Manager, Technical Information Center
RADIAH ROSE, Manager, Editorial Projects

Sponsors

U.S. DEPARTMENT OF DEFENSE U.S. ENVIRONMENTAL PROTECTION AGENCY COMMITTEE ON TOXICOLOGY

GARY P. CARLSON (*Chair*), Purdue University (retired), West Lafayette, IN
LAWRENCE S. BETTS, Eastern Virginia Medical School, Norfolk
DEEPAK K. BHALLA, Wayne State University, Detroit, MI

Members

DEBORAH A. CORY-SLECHTA, University of Rochester School of Medicine and Dentistry, Rochester, NY
MARY E. DAVIS, West Virginia University, Morgantown
DAVID C. DORMAN, North Carolina State University, Raleigh
MARGARET M. MACDONELL, Argonne National Laboratory, Argonne, IL
IVAN RUSYN, University of North Carolina, Chapel Hill, NC
KENNETH R. STILL, Portland State University, Portland, OR
JOYCE S. TSUJI, Exponent, Inc., Bellevue, WA

Staff

SUSAN N.J. MARTEL, Senior Program Officer for Toxicology
MIRSADA KARALIC-LONCAREVIC, Manager, Technical Information Center
RADIAH ROSE, Manager, Editorial Projects
TAMARA DAWSON, Program Associate

BOARD ON ENVIRONMENTAL STUDIES AND TOXICOLOGY[1]

ROGENE F. HENDERSON (*Chair*), Lovelace Respiratory Research Institute, Albuquerque, NM
PRAVEEN AMAR, Clean Air Task Force, Boston, MA
RICHARD A. BECKER, American Chemistry Council, Washington, DC
MICHAEL J. BRADLEY, M.J. Bradley & Associates, Concord, MA
JONATHAN Z. CANNON, University of Virginia, Charlottesville
GAIL CHARNLEY, HealthRisk Strategies, Washington, DC
DOMINIC M. DI TORO, University of Delaware Newark, DE
DAVID C. DORMAN, Department of Molecular Biomedical Sciences, Raleigh, NC
CHARLES T. DRISCOLL, JR., Syracuse University, New York
WILLIAM H. FARLAND, Colorado State University, Fort Collins, CO
LYNN R. GOLDMAN, George Washington University, Washington, DC
LINDA E. GREER, Natural Resources Defense Council, Washington, DC
WILLIAM E. HALPERIN, University of Medicine and Dentistry of New Jersey, Newark

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

Members

STEVEN P. HAMBURG, Environmental Defense Fund, New York, NY
ROBERT A. HIATT, University of California, San Francisco **PHILIP K. HOPKE**, Clarkson University, Potsdam, NY
SAMUEL KACEW, University of Ottawa, Ontario
H. SCOTT MATTHEWS, Carnegie Mellon University, Pittsburgh, PA
THOMAS E. MCKONE, University of California, Berkeley
TERRY L. MEDLEY, E.I. du Pont de Nemours & Company, Wilmington, DE
JANA MILFORD, University of Colorado at Boulder, Boulder **MARK A. RATNER**, Northwestern University, Evanston, IL
JOAN B. ROSE, Michigan State University, East Lansing, MI
GINA M. SOLOMON, California Environmental Protection Agency, Sacramento, CA
PETER S. THORNE, University of Iowa, Iowa City, IA **JOYCE S. TSUJI**, Exponent, Bellevue, WA

Senior Staff

JAMES J. REISA, Director
DAVID J. POLICANSKY, Scholar
RAYMOND A. WASSEL, Senior Program Officer for Environmental Studies
ELLEN K. MANTUS, Senior Program Officer for Risk Analysis
SUSAN N.J. MARTEL, Senior Program Officer for Toxicology **MIRSADA KARALIC-LONCAREVIC**, Manager, Technical Information Center
RADIAH ROSE, Manager, Editorial Projects

OTHER REPORTS OF THE BOARD ON ENVIRONMENTAL STUDIES AND TOXICOLOGY

Review of EPA's Integrated Risk Information System (IRIS) Process (2014)
Review of the Environmental Protection Agency's State-of-the-Science Evaluation of Nonmonotonic Dose–Response Relationships as They Apply to Endocrine Disruptors (2014)
Assessing Risks to Endangered and Threatened Species from Pesticides (2013)
Science for Environmental Protection: The Road Ahead (2012)
Exposure Science in the 21st Century: A Vision and A Strategy (2012)
A Research Strategy for Environmental, Health, and Safety Aspects of Engineered Nanomaterials (2012)
Macondo Well–Deepwater Horizon Blowout: Lessons for Improving Offshore Drilling Safety (2012)
Feasibility of Using Mycoherbicides for Controlling Illicit Drug Crops (2011)
Improving Health in the United States: The Role of Health Impact Assessment (2011)
A Risk-Characterization Framework for Decision-Making at the Food and Drug Administration (2011)
Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde (2011)
Toxicity-Pathway-Based Risk Assessment: Preparing for Paradigm Change (2010)
The Use of Title 42 Authority at the U.S. Environmental Protection Agency (2010)
Review of the Environmental Protection Agency's Draft IRIS Assessment of Tetrachloroethylene (2010)
Hidden Costs of Energy: Unpriced Consequences of Energy Production and Use (2009)
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 (sixteenth volumes, 2000-2014)
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

Potential Health Risks to DOD Firing-Range Personnel from Recurrent Lead

Exposure (2012)
Review of Studies of Possible Toxic Effects from Past Environmental Contamination at Fort Detrick: A Letter Report (2012)
Review of Risk Assessment Work Plan for the Medical Countermeasures Test and Evaluation Facility at Fort Detrick, A Letter Report (2011)
Assistance to the U.S. Army Medical Research and Materiel Command with Preparation of a Risk Assessment for the Medical Countermeasures Test and Evaluation (MCMT&E) Facility at Fort Detrick, Maryland, A Letter Report (2011)
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), Volume 9 (2010), Volume 10 (2011), Volume 11 (2012), Volume 13 (2012), Volume 14 (2013), Volume 15 (2013), Volume 16 (2014)
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 more than 270 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 seventeenth vol

ume in that series. AEGL documents for acrylonitrile, carbon tetrachloride, cyanogen, epichlorohydrin, ethylene chlorohydrin, toluene, trimethylacetyl chloride, hydrogen bromide, and boron tribromide are each published as an appendix in this report. 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.

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

The committee's review of the AEGL documents involved both oral and written presentations to the committee by the 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 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 committee interim reports, which summarize the committee's conclusions and recommendations for improving NAC's AEGL documents for acrylonitrile (interim reports 19b, 21a, and 22), carbon tetrachloride (interim reports 13, 14, 18, and 22), cyanogen (interim report 19a), epichlorohydrin (interim reports 15, 19a, 20a, and 21a), ethylene chlorohydrin (interim reports 20a and 21a), toluene (interim reports 12, 18, and 22), trimethylacetyl chloride (interim reports 20a and 21a), hydrogen bromide (interim reports 16, 18, and 22), and boron tribromide (interim reports 19a and 22): Deepak Bhalla (Wayne State University), Harvey Clewell (The Hamner Institutes for Health Sciences), Jeffrey Fisher (U.S. Food and Drug Administration), David Gaylor (Gaylor and Associates, LLC), Sam Kacew (University of Ottawa), A. Wallace Hayes (Harvard School of Public Health), Rogene Henderson (Lovelace Respiratory Research Institute [retired]), James McDougal (Wright State University [retired]), Charles Reinhardt (DuPont Haskell Laboratory [retired]), Andrew Salmon (California Environmental Protection Agency), Joyce Tsuji (Exponent, Inc.), Bernard Wagner (New York University Medical Center [retired]), and Judith Zelikoff (New York University).

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 re

lease. The review of interim reports was overseen by David Gaylor (Gaylor and Associates, LLC), Sidney Green, Jr., (Howard University), and Robert Goyer (University of Western Ontario [retired]). 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 Ernest Falke and Iris A. Camacho from EPA. The committee also acknowledges Susan Martel, the project director for her work this project. Other staff members who contributed to this effort are James J. Reisa (director of the Board on Environmental Studies and Toxicology), Radiah Rose (manager of editorial projects), Mirsada Karalic-Loncarevic (manager of the Technical Information Center), 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.

Edward C. Bishop, *Chair*
Committee on Acute Exposure
Guideline Levels

Contents

Acute Exposure Guideline Levels for Selected Airborne Chemicals

VOLUME 17

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

This report is the seventeenth 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 and 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)[3] 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

[3] NAC completed its chemical reviews in October 2011. The committee was composed of members from EPA, DOD, many other federal and state agencies, industry, academia, and other organizations. From 1996 to 2011, the NAC discussed over 300 chemicals and developed AEGLs values for at least 272 of the 329 chemicals on the AEGLs priority chemicals lists. Although the work of the NAC has ended, the NAC-reviewed technical support documents are being submitted to the NRC for independent review and finalization.

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 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) chemicalphysical 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 noobserved-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 were initially prepared by ad hoc AEGL development teams consisting of a chemical manager, chemical reviewers, and a staff scientist of the NAC contractors—Oak Ridge National Laboratory and subsequently SRC, Inc. The draft documents were then reviewed by NAC and elevated from "draft" to "proposed" status. After the AEGL documents were approved by NAC, they were published in the *Federal Register* for public comment. The reports were 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 committee 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 and the contractors for the accuracy and completeness of the toxicity data cited in the AEGL reports. Thus far, the committee has prepared sixteen reports in the series *Acute Exposure Guideline Levels for Selected Airborne Chemicals* (NRC 2001b, 2002b, 2003, 2004, 2007b, 2008b, 2009, 2010a,b, 2011, 2012a,b,c, 2013a,b, 2014). This report is the seventeenth volume in that series. AEGL documents for acrylonitrile, carbon tetrachloride, cyanogen, epichlorohydrin, ethylene chlorohydrin, toluene, trimethylacetyl chloride, hydrogen bromide, and boron tribromide are each published as an appendix in this report. 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). 2010a. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 8. Washington, DC: The National Academies Press.

NRC (National Research Council). 2010b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 9. Washington, DC: The National Academies Press.

NRC (National Research Council). 2011. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 10. Washington, DC: The National Academies Press.

NRC (National Research Council). 2012a. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 11. Washington, DC: The National Academies Press.

NRC (National Research Council). 2012b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 12. Washington, DC: The National Academies Press.

NRC (National Research Council). 2012c. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 13. Washington, DC: The National Academies Press.

NRC (National Research Council). 2013a. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 14. Washington, DC: The National Academies Press.

NRC (National Research Council). 2013b. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 15. Washington, DC: The National Academies Press.

NRC (National Research Council). 2014. Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 16. Washington, DC: The National Academies Press.

Appendixes

6

Toluene[4]

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 are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or 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

[4] This document was prepared by the AEGL Development Team composed of Sylvia Talmage (Oak Ridge National Laboratory), Chemical Manager George Woodall (National Advisory Committee [NAC] on Acute Exposure Guideline Levels for Hazardous Substances), and Ernest V. Falke (U.S. Environmental Protection Agency). 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 guidelines 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 concentrations 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 AEGL values represent threshold concentrations 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

Toluene is a widely used raw material in the chemical manufacturing industry. It is a component of automotive and aviation gasoline and a solvent in lacquers, paint thinners, glue, and other household products. A major concern with the uncontrolled release of toluene is explosion and fire.

The odor threshold for toluene ranges from 0.16 to 100 ppm for detection and 1.9 to 69 ppm for recognition; the odor is not unpleasant. Toluene is readily absorbed by the respiratory tract and distributed throughout the body, accumulating in tissues with high lipid content. Liquid toluene can be absorbed through intact skin and the alimentary tract. Toluene is a central nervous system (CNS) depressant and is irritating to the eyes at high concentrations. Other effects observed in humans after accidental or intentional inhalation of high concentrations of toluene include renal toxicity, cardiac arrhythmias, hepatomegaly, and developmental abnormalities. Considerable human and animal toxicity data were available for deriving AEGL values.

Clinical, metabolism, and occupational-monitoring studies were available for deriving AEGL-1 values. Many of the studies evaluated sensory irritation and CNS depression. Numerous studies of neurotoxicity have also been conducted in rodents. Lethality data on toluene were available for the mouse and rat.

AEGL-1 values were based on the preponderance of data from clinical and occupational studies and from metabolism studies of human subjects that indicated that an 8-h exposure to toluene at 200 ppm is near a threshold for AEGL-1 effects (headache), and also near a level for detectable neurologic effects

(moderate lightheadedness and increased simple reaction time). More than 300 indi-

viduals have been evaluated in 20 clinical studies that involved exposures to toluene at 40-700 ppm, and several thousand workers were surveyed in occupational-monitoring studies that involved exposures at up to 1,500 ppm. Those populations are presumed to be composed of healthy individuals, but they represent a broad spectrum of uptake rates (sedentary, working, and exercise conditions) and individual differences in metabolism rates (Gamberale and Hultengren 1972; Veulemans and Masschelein 1978; Brugnone et al. 1986; Hjelm et al. 1988). Although many clinical studies tested toluene at 100 ppm, the addition of exercise to the protocol in the studies of Astrand et al. (1972), Baelum et al. (1990), and Rahill et al. (1996) more than doubled the toluene blood concentration; concentrations were greater than that from a 200-ppm exposure with the subject at rest (Astrand et al. 1972; Veulemans and Masschelein 1978).

The weight of evidence from these studies indicates that an 8-h exposure to toluene at 200 ppm was without adverse health effects in the tested populations, and was an appropriate basis for the AEGL-1 values. At concentrations of 80-200 ppm, toluene approaches a steady-state in the blood within 15-30 min (Astrand et al. 1972; Carlsson 1982). Storage takes place in lipid-rich tissues (including the brain), but elimination is rapid. Toluene reaches a steady-state in the blood and brain fairly rapidly, and no cumulative effects were observed after repeated exposure at 100 ppm for 5 days (Stewart et al. 1975); therefore, 200 ppm was used as the basis for all AEGL-1 durations. Although there was no notable discomfort and only mild irritation (effects expected to be concentration dependent and not subject to changes in activity level), headaches (potentially related to CNS effects), dizziness, and measurable neurologic effects were reported after exposure to toluene at 100-200 ppm. Neurologic effects would be expected to be affected by an increase in activity level, leading to higher concentrations in the brain (target tissue for CNS effects). As noted earlier, physical activity may double the blood concentration of toluene. On the basis of the range of alveolar concentrations among humans exposed to anesthetic gases, an uncertainty factor of 3 for human variability was applied to calculate an AEGL-1 value of 67 ppm for all durations. That concentration is deemed protective for all observed effects, including those at 100-200 ppm.

The AEGL-2 values for toluene are based on impaired neurologic function that affects the ability to escape. The point of departure was a no-observedadverse-effect level (NOAEL) of 1,600 ppm for a doubling of the choice reaction time in Long-Evans rats exposed for 34 min (Bushnell et al. 2007a). The CNS effects observed during exposure were assumed to be directly related to parent material reaching the brain. Therefore, the toluene concentration in brain (BrTC) after 34 min provides an internal dose measurement correlating with the NOAEL. The physiologically-based pharmacokinetic (PBPK) model of Kenyon et al. (2008)

was used to calculate the internal dose or BrTC in the rat. An interspecies uncertainty factor of 1 was applied because pharmacokinetic modeling eliminated the toxicokinetic component of the uncertainty factor, and the pharmacodynamic component was assigned a value of 1 because similar effects (CNS depression) were observed in humans and animals. An intraspecies uncertainty factor of 3 was applied because the minimum alveolar concentration for volatile anesthetics should not vary by more than 2- to 3-fold among humans. A human model for toluene (Benignus et al. 2006) was then used to determine the exposure concentrations at each of the AEGL exposure durations that would yield the same brain concentration in humans.

Further support for the AEGL-2 values is provided by comparisons with the results obtained from the published model of Benignus et al. (2009, 2011), which calculates the BrTC leading to an effect level comparable to an individual with a blood ethanol level of 0.10% (the legal level of incapacitation in the United States). Although the routes of exposure are different between the two chemicals (inhalation for toluene inhalation and oral for ethanol), the relative effect levels are relevant for comparison purposes.

The AEGL-3 values for toluene were based on a NOAEL for lethality in rats. A 2-h exposure to toluene at 6,250 ppm was not lethal but produced prostration in rats (Mullin and Krivanek 1982). A 2-h exposure of rats at 10,000 ppm resulted in 20% mortality (Kojima and Kobayashi 1973). The same PBPK models and uncertainty factors that were used to derive the AEGL-2 values were used to calculate the AEGL-3 values.

The AEGL values for toluene are presented in Table 6-1.

TABLE 6-1 AEGL Values for Toluene

Classification	10 min	30 min	1 h	4 h	8 h	End Point (Reference)
AEGL-1 (nondisabling)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	No-effect level for notable discomfort and neurologic effects in 20 clinical studies.[a]
AEGL-2 (disabling)	1,400 ppm[b] (5,300 mg/m^3)	760 ppm (2,900 mg/m^3)	560 ppm (2,100 mg/m^3)	310 ppm (1,200 mg/m^3)	250 ppm (940 mg/m^3)	No-effect level for impaired ability to escape, decrement in neurological function.[c]
AEGL-3 (lethal)	_[d]	5,200 ppm[b] (20,000 mg/m^3)	3,700 ppm[b] (14,000 mg/m^3)	1,800 ppm[b] (6,800 mg/m^3)	1,400 ppm[b] (5,300 mg/m^3)	No-effect level for lethality in rats (Mullin and Krivanek 1982)

[a] Clinical studies include Astrand et al. (1972), Gamberale and Hultengren (1972), Stewart et al. (1975), and Baelum et al. (1990). [b] Concentration is one-tenth or more of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, safety considerations against the hazard of explosion must be taken into account.

[c] No-effect level for a doubling in choice reaction time in rats (Bushnell et al. 2007a). Effect level supported by comparison of toluene inhalation with ethanol consumption in humans (Benignus et al. 2011).

[d] The 10-min AEGL-3 value of 10,000 ppm (38,000 mg/m^3) is higher than 50% of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

1. INTRODUCTION

Toluene is a colorless, flammable liquid with a pungent floral or aromatic odor similar to that of benzene (Henderson 2001). The odor has also been described as sour or burnt (Hellman and Small 1974), rubbery, or similar to that of moth balls (Billings and Jonas 1981; Ruth 1986). The chemical and physical properties of toluene are presented in Table 6-2.

A major concern with the uncontrolled release of toluene is explosion and fire. The flash point of toluene is 4.4°C and the ignition temperature is 536°C. The saturated vapor is only slightly heavier (about 10% more) than air and may travel a considerable distance in still air to a source of ignition and flash back. Toluene may be rapidly dispersed by normal eddy currents. The vapor may explode if ignited in an enclosed area (Weiss 1980). For example, a fatal explosion occurred when workers were sawing an opening in the side of an empty 10,000gallon toluene storage tank (NIOSH 1985).

TABLE 6-2 Chemical and Physical Properties of Toluene

Parameter	Value	Reference
Synonyms	Methyl benzene; phenyl methane; methyl benzol; monomethyl benzene; toluol; methacide; tolu-sol; antisal 1a	ATSDR 2000
CAS registry no.	108-88-3	O'Neil et al. 2006
Chemical formula	C_7H_8	O'Neil et al. 2006
Molecular weight	92.140	O'Neil et al. 2006
Physical state	Clear liquid	O'Neil et al. 2006
Boiling point	110.6°C	O'Neil et al. 2006
Density/specific gravity	0.866 g/cm^3	O'Neil et al. 2006
Solubility in water	Slightly soluble, 0.067%	O'Neil et al. 2006
Vapor density (air = 1)	3.1	Henderson 2001

Vapor pressure	36.7 mmHg	Henderson 2001
Log K_{ow}	2.72	ATSDR 2000
Flash point	4.4°C (closed cup) 12.8°C (open cup)	O'Neil et al. 2006 Weiss 1980
Flammability limits		Henderson 2001
Lower explosive limit	1.4%	
Upper explosive limit	7.9%	
Conversion factors in air	1 ppm = 3.77 mg/m^3 1 mg/m^3 = 0.265 ppm	NIOSH 2011

In 1999, world production of toluene was nearly 13,000,000 tons. Approximately 79% of total production is from catalytic reforming of refinery streams, an additional 16% is separated from pyrolysis gasoline, and 4% is produced via separation from coal tars. Most of the toluene produced (85-90%) is not isolated but remains as a benzene-toluene-ethylbenzene-xylene (BTEX) mixture for use in gasoline as an octane booster. Of the remaining capacity, the primary use is for chemicals and solvents such as benzene (via dealkylation). In the chemical industry, toluene is used as raw material in the production of benzyl chloride, benzoic acid, phenol, cresols, vinyl toluene, trinitrotoluene (TNT), and toluene diisocyanate. Approximately 14% of toluene is also used as a solvent for paints and coatings and in adhesives, inks, and pharmaceuticals (US Air Force, 1989; EPA, 1990; Ozokwelu 1997; Chemical Week 2000).

In the past, commercial toluene contained benzene and xylenes at up to 2-15% and 10%, respectively (NIOSH 1973; Low et al. 1988). Highly purified toluene (benzene at less than 0.01%) began to be produced commercially in 1973. Therefore, greater consideration was given to more recent toxicity studies, in which the toluene is more chemically pure.

For both the general population and for occupationally-exposed individuals, inhalation is the primary route of exposure to toluene. Evaporation of gasoline and automobile exhaust is the largest source of toluene in the environment, and industries that use toluene as a solvent are the second largest source (EPA 1990). Toluene is also a common indoor-air contaminant due to releases from common household products and from cigarette smoke (ATSDR 2000).

2. HUMAN TOXICITY DATA

The typical sequence of events that result from exposure to toluene at concentrations high enough to produce unconsciousness include euphoria, delusions, and sedation (Benignus 1981; Bruckner and Warren 2001). Mood elevation, nausea, and subtle changes in performing intricate tasks have been reported at 200 ppm and higher (ACGIH 2005), although some of the studies are poorly documented (see Table 6-3). Exposure to toluene may be occupational or recreational; in the latter case it is reported to produce a pleasant euphoria with

few side effects (Massengale et al. 1963). Its abuse potential may be enhanced by its apparent low irritancy in humans (von Oettingen et al. 1942; Carpenter et al. 1944; Nielsen and Alarie 1982).

The major effect of toluene is its narcotic effects, manifested in muscular weakness, incoordination, and mental confusion (NIOSH 1973). Adverse effects on the liver, kidneys, lungs, and heart are limited to acute and chronic exposures at high vapor concentrations. Early reports suggesting deleterious effects on the bone marrow involved the use of toluene contaminated with benzene (NIOSH 1973). The health effects of toluene have been reviewed by Cohr and Stockholm (1979), NRC (1981, 2008), WHO (1985), CIR (1987), Low et al. (1988), EPA (1990), ATSDR (2000), Bruckner and Warren (2001), and Henderson (2001).

TABLE 6-3 Sensory and Neurobehavioral Effects of Toluene in Controlled Human Studies

Concentration (ppm)	Duration	Subjects/Effects	Reference
10, 40, 100	6 h	16 males (21-32 y): slight irritation of eyes and nose at 100 ppm; no effect on mood, fatigue, or sleepiness; increased frequency of headache, dizziness, and feeling of slight to moderate intoxication; no effect on pulmonary function or nasal mucous flow; no significant effect on performance in eight psychomotor tests.	Andersen et al. 1983
40	4 h	12 males (20-50 y): no effects on measures of motor performance, attention, perceptual coding and memory, or mood.	Lammers et al. 2005a
110	Three 30-min peaks over 4 h		
50[a]	3 h	10 males, 20 females (19-45 y): no subjective symptoms.	Luderer et al. 1999
50	4.5 h	20 males: no increase in sleepiness; increase in scores of unpleasant smell and irritation to the throat.	Muttray et al. 2005
80	4 h	8 males (22-50 y): no impairment on neurobehavioral tasks.	Cherry et al. 1983
80	4 h	16 males (23-38 y): no differences in subjective symptoms compared with controls; no impairment in tests of simple reaction time, short-term memory, or choice reaction time; no effect on heart rate.	Olson et al. 1985
80	4.5 h	12 males (22-44 y): increase in subjective symptoms (nausea, headache, irritation), but rated negligible; no impairment in tests of simple and choice reaction time, color-word vigilance, or memory; no effect on heart rate, electroencephalograph results, or sleep latency.	Iregren et al. 1986
100	3.5 h	18 subjects: no behavioral deficits in psychomotor tests.	Winneke 1982

(Co

ntin

ued)

TABLE 6-3 Continued

Concentration (ppm)	Duration	Subjects/Effects	Reference
100	4 h		
100	6 h		
100	6.5 h (printers were previously exposed for 9 to 25 y)	30 males and females: no serious impairment in neurobehavioral tests (small impairment in one measure of a visual-vigilance test). 6 males and females (27-38 y): No significant effect on pulmonary function (subjects exercised for 30 min); slight effect on some multitask and neuropsychologic tests (increased latency but not accuracy on neurobehavioral tasks); no symptoms reported in a double-blind questionnaire.	
100	1, 3, or 7.5 h/d for 5 d	43 male printers and 43 referents (29-50 y). Four groups tested (two exposed and two controls): sensory irritation (no annoyance or nausea); sleepiness; fatigue; slightly decreased performance on four of 10 tests (manual dexterity, color discrimination, visual perception) in one or both exposed groups; no changes in renal function.	
100 (constant) or 100 (TWA; exposure varied with peaks of 300 ppm every 30 min)	7 h (three 15-min exercise periods; both exposures)	10 males and 9 females (19-47 y): no decrement in psychomotor-test results on first day of exposure; slight decrement in performance in tests involving visual vigilance and tone detection on days 2 and 5 in females exposed for 7.5 h; similar subjective symptoms between exposed and control groups.	
75, 150	7 h/d for 3 d	32 males and 39 females (31-50 y): sensory irritation of nose and lower airways; increase in dizziness and feeling of intoxication; slight decrement in one of four psychomotor-performance tests; no differences in symptoms or performance found between constant and varying exposures.	
		42 male and female students (18-35 y): 7% (mean) decrement in several neurobehavioral tests at 150 ppm; slight increases in headache, ocular irritation; sleepiness on first day; CNS	

		effect demonstrated by dose-response in number of times subjects slept. No clear pattern of neurobehavioral effects. Variation in the control data across 3 d was greater than with toluene.	Stewart et al. 1975
Dick et al. 1984			
Rahill et al. 1996			Baelum et al. 1990
Baelum et al. 1985; Nielsen et al. 1985			Echeverria et al. 1989; 1991
100, 200[a]	30, 60 min	11 males and 4 females (18-46 y): no difference in heart rate, pulmonary ventilation, oxygen consumption, or blood lactate, either at rest or during a work load of 50 W.	Astrand et al. 1972; Astrand 1975
100, 200	3 h or 7 h with 1-h break	23 males (23 y, average age): decrease in pulse rate at 200 ppm for 3 h; tendency to have prolonged reaction time at 200 ppm; no clear concentration-response relationship.	Ogata et al. 1970
100, 300, 500, 700[a]	Successive 20-min exposure at increasing concentrations (one 5-min break); total 85 min.	12 males (20-35 y): no effect on reaction time or perceptual speed at 100 ppm; increase in simple reaction time at 300 ppm; increase in complex reaction time at 500 ppm; decrease in perceptual speed at end of exposure at 700 ppm; no effect on heart rate during total exposure; one of 12 subjects able to distinguish between control and toluene exposures.	Gamberale and Hultengren 1972
220[b] 427[b]	15 min 15 min	6/6 subjects willing to work for 8 h; negligible sensory symptoms. 3/6 subjects willing to work for 8 h; 2 subjects reported slight "lightheadness"; 1 reported a "stuffy, drowsy feeling."	Carpenter et al. 1976
200	6 h	5 males, resting: no change in respiration; increased heart rate.	Suzuki 1973
240	Three 30-min sessions	11 males (20-21 y): impaired vigilance in third session; decreased fatigue during second session.	Horvath et al. 1981

[a] Subjects exposed via a mouthpiece.
[b] Measured as toluene in "toluene concentrate."

2.1. Acute Lethality

Inhalation of "high concentrations" can result in paresthesia, vision disturbances, dizziness, nausea, CNS depression, and collapse (Henderson 2001). Most deaths involve solvent abuse or "glue sniffing", which involves sniffing a mixture of solvents from a plastic bag to concentrate the vapors. Solvents, such as paint thinners, may contain as much as 99% toluene (Donald et al. 1991). Prior to 1975, an estimated 125 deaths involving solvent abuse occurred per year in the United States (Winek and Collom 1975). Few deaths have been attributed solely to the inhalation of pure toluene, but are associated with paint thinners, spray paints, glues, and other products containing toluene. Few data are available on the concentrations of toluene that caused deaths in these studies. The concentration of toluene achieved when inhaling directly from a paper bag containing gauze soaked with toluene from a tube of polystyrene cement is estimated to be 10,000 ppm (Press and Done 1967). According to the authors, this concentration causes unconsciousness within a few minutes, which results in cessation of exposure.

Bass (1970) reviewed reports of "sudden sniffing death syndrome." Eyewitness accounts of the events prior to death were similar and included: inhalation of volatile hydrocarbons from a bag, panic, physical exertion (usually involving running), and sudden collapse and death. This pattern was characterized by the author as being the result of severe cardiac arrhythmia associated with fulminate pulmonary edema, the excitement of a light plane anesthesia, hyperadrenergic crisis, or some combination of these and possibly unknown factors. The author suggests a mechanism of action involving sensitization of the myocardium by volatile hydrocarbons and subsequent physical exertion coalescing to produce sudden and severe arrhythmia. No cardiac-sensitization tests of toluene in dogs was found, but dogs exposed to toluene at 30,000 ppm for 9-10 min died of ventricular fibrillation and severe hypoxia (Ikeda et al. 1990; see Section 3.1.1).

2.2. Nonlethal Toxicity

The odor threshold of toluene in air ranges between 2 and 40 ppm (Amoore and Hautala 1983; Ruth 1986). According to Hellman and Small (1974), the odor can be detected at 0.17 ppm and recognized at 1.74 ppm. The American Industrial Hygiene Association (AIHA1989) reports the detectable range as 0.16-100 ppm and the odor recognition range as 1.9-69 ppm. According to a literature survey (Ruth 1986), the threshold for "irritation" is 200 ppm. In a more recent series of studies, the odor threshold and thresholds for ocular and nasal irritation were measured using squeeze bottles and a two-alternative, forced-choice procedure with an ascending method of limits (Cometto-Muniz and Cain 1995; Abraham et al. 1996). Thresholds for ocular irritation and nasal pungency were approximately

>20,000 and 29,850 ppm, respectively. The nasal pungency threshold was developed with anosmics (subjects who were clinically diagnosed as lacking a sense of smell and were, thus, unbiased by odor sensations).

Solvent abusers repeatedly inhale anesthetizing concentrations on a daily basis. Toluene abuse, an extreme form of exposure, has resulted in myocardial infarction and cardiac effects (Cunningham et al. 1987; Wiseman and Banim 1987; Carder and Fuerst 1997), renal toxicity that includes renal tubular acidosis (Taher et al. 1974; Reisin et al. 1975; Patel and Benjamin 1986; Gupta et al. 1991; Kamijima et al. 1994), metabolic acidosis often with "anion gap" (the sum of the cations in the blood minus the sum of the anions in the blood) (Fischman and Oster 1979; Jone and Wu 1988), acute encephalopathy in children (8-14 years old) (King et al. 1981), and cerebellar ataxia (Boor and Hurtig 1977). Streicher et al. (1981) described syndromes of toluene sniffing in adults, which included a pattern of three dominant symptoms: muscle weakness, gastrointestinal disorders, and neuropsychiatric disorders. Neuropsychiatric symptoms included headache, dizziness, syncope, paresthesias or peripheral neuropathy, hallucinations, lethargy, and cerebellar ataxia. Some exposures were to mixtures of solvents and ethanol. Exposure concentrations could not be ascertained. In a review of neurologic and psychiatric consequences of toluene abuse, Ron (1986) concluded that evidence for such sequelae remains inconclusive.

Distal renal tubular acidosis is an established consequence of toluene abuse and has been reported in numerous studies. This consequence is notable with the extremely high vapor concentrations associated with chronic abuse situations (O'Brien et al. 1971; Taher et al. 1974; Fischman and Oster 1979; Kroeger et al. 1980; Moss et al. 1980; Russ et al. 1981; Streicher et al. 1981; Patel and Benjamin 1986; Marjot and McLeod 1989). In life-threatening cases, patients present with severe generalized muscle weakness, nausea and vomiting, and neuropsychiatric derangements (Streicher et al. 1981; Marjot and McLeod 1989). The mechanism of action for this disorder is discussed in Section 4.2. In spite of reports of hepatic, adrenal, and renal damage, there appears to be a low incidence of these injuries among glue sniffers. Only modest elevations of serum glutamic-oxaloacetic transaminase and alkaline phosphatase and transient abnormalities in urinalyses were observed among groups of glue sniffers (Press and Done 1967; Litt et al. 1972; Weisenberger 1977).

2.2.1. Occupational Exposures

Studies of workers exposed to toluene in occupational settings have focused on functional impairment. These exposures are usually not of a magnitude required to produce serious sustained effects. Even though exact exposure parameters of concentration and duration are usually not determined in these studies, the investigations provide information about the more common effects

and at what approximate concentrations these effects are observed. Interpretation of most occupational exposure studies of toluene is confounded by co-exposure to other solvents. Only the study by Wilson (1943) addressed acute effects immediately following the work day. Additional occupational monitoring studies are briefly discussed below.

Wilson (1943) surveyed the effects of various concentrations of toluene in workers at a large industrial plant. Approximately 1,000 workers were exposed to toluene at concentrations of 50-1,500 ppm for periods of 1-3 weeks. Approximately 10% of the employees had symptoms severe enough to require examination at a hospital. The employees were grouped according to the concentration of toluene fumes measured at their job sites; measurements were made with a combustible gas indicator. (Combustible gas indicators measure all combustibles and are generally incapable of measuring concentrations of less than 5%.) In workers exposed to toluene at 200 ppm or lower, the most common complaints were headache, lassitude, and loss of appetite. At 200-500 ppm, complaints included headache, lassitude, and anorexia that were more pronounced. These subjects also complained of nausea, a bad taste in the mouth, loss of coordination, decreased reaction time, and momentary loss of memory. At concentrations greater than 500 ppm, the major complaints were nausea, headache, dizziness, anorexia, palpitation, and extreme weakness. Physical and laboratory examinations of the approximately 60 workers exposed to toluene at 200 ppm or lower were negative. Also, no significant physical or laboratory findings were noted for the 30 workers exposed at 200-500 ppm. Physical examination of the remaining 10%, exposed at 500 ppm or higher, found loss of coordination, decreased reaction time, and petechiae under the skin. Laboratory results from these patients revealed low erythrocyte counts and leukopenia, and bone marrow biopsy demonstrated aplastic anemia in two subjects. The hospitalized workers were treated symptomatically. No deaths occurred. The analytic methodology in this study and the confounding issue of benzene exposure precludes the use of this study for developing AEGL values.

Monitoring studies show that workers have been routinely exposed to toluene at 32 ppm (0.1-457 ppm) (Neubert et al. 2001b); a lifetime weighted average of 45 ppm (Seeber et al. 2005); a time-weighted average (TWA) of 63-118 ppm (5-353 ppm) (Ovrum et al. 1978); a TWA of 88 ppm (49-130 ppm) (Foo et al. 1990); 50-100 ppm (Neubert et al. 2001a); 50-150 ppm (Iregren 1982); ≥100 ppm (Ukai et al. 1993); an estimated average of 117 ppm (Juntunen et al. 1985); 132 ppm (66-250 ppm) (Zavalic et al. 1998); 1->100 ppm (Lee et al. 1988); 100440 ppm with peak values of 200-500 ppm (Eller et al. 1999); 9-467 ppm (Deschamps et al. 2001); ≥200 ppm (Forni et al. 1971); 200-800 ppm (Parmeggiani and Sassi 1954); and ≤ 500 ppm (Greenberg et al. 1942). In most cases when psychomotor tests were performed, the tests were administered before the workday; therefore, acute effects were not measured. In most of these studies, only subtle differences in neurologic parameters, such as alterations in the visual

evoked response or small decreases in reaction time, were found compared with control groups (Yin et al. 1987; Foo et al. 1990; Abbate et al. 1993; Murata et al. 1993; Vrca et al. 1995; Boey et al. 1997; Zavalic et al. 1998; Eller et al. 1999). Seeber et al. (2005) found no evidence of neurobehavioral effects following long-term exposure to toluene below 50 ppm. Irritation of the conjunctiva and upper respiratory tract was found in only one of 11 workers exposed at 200-800 ppm (Parmeggiani and Sassi 1954). In some studies, incidences of subjective symptoms, such as sore throat, were greater than in matched control groups (Tanaka et al. 2003). Symptoms correlated with duration and extent of exposure in some studies (Lee et al. 1988) but not in others (Gericke et al. 2001). Chronic exposures of workers to toluene at low concentrations have not resulted in alterations in liver-enzyme activity or hormone concentrations (Gericke et al. 2001) or in serious renal damage (ATSDR 2000). An acute exposure of flexoprint workers to toluene at approximately 100 ppm for 6.5 h failed to show significant changes in β-microglobulin or albumin excretion compared with air-exposed controls (Nielsen et al. 1985).

Studies of occupationally-exposed workers indicate that chronic exposure to toluene at low concentrations results in hearing loss (Morata et al. 1997; ATSDR 2000). However, in a study of 333 rotogravure printing workers, exposure at less than 50 ppm could not be related to ototoxicity (Schaper et al. 2003). In animal models, toluene was shown to damage outer hair cells in rats exposed to toluene at 1,400 ppm for 14 h/day for 8 days (Johnson and Canlon 1994; see also Section 3.2.2). A question of whether toluene impaired color vision in workers was raised by Zavalic et al. (1998). Color vision was impaired in these workers, but alcohol and age were confounding factors.

2.2.2. Accidental Exposures

Two men working with toluene to remove excess glue from tiles in a swimming pool were exposed to toluene at concentrations greater than 1,842 ppm for 2 or 3 h (Meulenbelt et al. 1990). The concentration of toluene was measured at the edge of the pool by Drager tube 3 h after the men were rescued. Concentrations were presumed to be higher at the bottom of the pool where the men were found because toluene is heavier than air and would have accumulated at the bottom of the pool. Both men were disoriented when found; one was unable to walk or sit, and the other was barely able to walk. Physical examinations carried out 1 h after they were found revealed mucosal irritation of the eyes, slurred speech, headache, paresis, and amnesia. The patient exposed for 3 h had an excessive anion gap and a sinus bradycardia. The second patient, who was exposed for 2 h, complained of headache, and clinical examination revealed a sinus tachycardia and a slightly excessive anion gap. Neither patient showed abnormalities in hepatic function or hematologic parameters. Blood toluene

concentrations taken 2 h after exposure were 4.1 and 2.2 mg/L in the patients exposed for 3 and 2 h, respectively. The most striking effect of this acute exposure was the increased anion gap in both patients, which the authors attributed to either the high plasma concentration of toluene metabolites (benzoic acid and/or hippuric acid) or distal tubular acidosis. Recovery for both patients appeared complete at the 1-week postexposure medical examination.

Two cases of accidental occupational exposure to toluene at very high concentrations were reported by Longley et al. (1967). One of the case reports involved several men who were exposed to toluene in an enclosed space aboard a commercial ship. Initially, two men were assigned to spray ballast tanks with an "anti-rust" paint containing toluene. One man climbed out of the tank because he felt dizzy, and shortly afterwards noticed that the other man had collapsed. Seventeen more men suffered symptoms of exposure during rescue operations, which lasted for about 2 h. Symptoms of exposure included unconsciousness, severe mental confusion, amnesia, and illogical behavior. All affected workers recovered fully within 30 min after breathing oxygen. No estimate of the toluene concentrations was possible.

The second incident also took place on a merchant ship (Longley et al. 1967). An accidental exposure to a concentrated insecticide containing malathion (20%), piperonyl butoxide (8%), pyrethrum (1.5%), and toluene (to 100%) occurred. Thirty gallons of this mixture, which contained 21 gallons of toluene, was mistakenly sprayed undiluted into a hold with a volume of about 102,000 cu. ft. within about 75 min. Seven men, including the workers and rescuers, were overcome, and three lost consciousness. The men were taken off the ship and given medical examinations. Because the cholinesterase activity of the men remained at 100%, the authors judged that the malathion was not absorbed appreciably. Using a Department of Scientific and Industrial Research (DSIR) pump which was designed by the British Department of Scientific and Industrial Research to make spot determinations of hazardous atmospheres, the toluene concentrations were estimated to be 5,000-10,000 ppm. However, calculations of the distribution of the 21 gallons of toluene in the hold results in approximate concentrations of 10,000-12,000 ppm. Because the vapor rapidly anesthetized the kneeling worker but not for a standing one, the concentrations were probably higher near the floor than at head level. Therefore, some sources estimate or report that the concentrations of toluene were 10,000 ppm at waist level and 30,000 ppm at floor level (NIOSH 1973; NRC 1981). In addition to unconsciousness, the men also suffered nausea, incoordination, amnesia, and feelings of intoxication, but they did not complain of ocular or throat irritation. The exposed men recovered without persistent effects.

2.2.3. Clinical Studies

Numerous clinical studies have been conducted with healthy human subjects exposed in controlled settings to monitored concentrations of toluene for varying durations. Studies performed in the 1940s are now considered compromised because toluene was less pure at that time and contained other solvents, including benzene, and limited analytic characterization of exposure concentrations were available. However, there are recent, well-conducted clinical studies of toluene that are suitable for estimating AEGL values (Table 6-3).

More than 300 individuals have been evaluated in clinical studies involving toluene exposures of 40-700 ppm. The subjects are presumed to be healthy individuals, but represent a broad spectrum of uptake rates (sedentary, working, and exercise conditions). Although many clinical studies used a toluene concentration of 100 ppm, the addition of exercise to the protocol in the studies of Astrand et al. (1972), Baelum et al. (1990), and Rahill et al. (1996) more than doubled the blood concentration of toluene to a level greater than that from a 200-ppm exposure with the subjects at rest (Astrand et al. (1972; Veulemans and Masschelein 1978). Baelum et al. (1990) investigated peak exposures of 300 ppm (14 times during a 7-h exposure; mean concentration of 100 ppm) with exercise (50-100 W) undertaken for 15 min during three of the peak exposures.
Astrand et al. (1972) also incorporated exercise into the 200-ppm exposures.

These studies generally addressed the threshold for subjective and CNS effects to set guidelines for chronic exposures. Some of these studies provide information on the threshold for subtle psychomotor dysfunction (impairment of mental traits, abilities, and processes) in humans. Several studies also addressed air quality and odor adaptation or olfactory fatigue. Although slight irritation involving the eyes and nose in humans was reported in several studies of toluene at 80-100 ppm, toluene is not a primary respiratory irritant as evidenced by the high RD_{50} (concentration the reduces respiratory rate by 50%) of 5,300 ppm (see Section 3.2.3). In general, complaints increased among control subjects, especially in studies with long exposure durations. Other studies reported exposures at 80-100 ppm to be nonirritating (Stewart et al. 1975; Cherry et al. 1983; Olson et al. 1985; Rahill et al. 1996). No CNS effects were reported at 80-100 ppm in studies of Winneke (1982), Cherry et al. (1983), and Stewart et al. (1975); effects were minor in other studies at 100-700 ppm (Gamberale and Hultengren 1972; Dick et al. 1984; Baelum et al. 1990). There were no biologically significant pulmonary or cardiovascular effects at 100 and 200 ppm for exposures up to 6 h (Astrand et al. 1972; Suzuki 1973) and no indications of renal damage (Nielsen et al. 1985). Exposure to toluene at 100 ppm in the study by Stewart et al. (1975) was repeated for 5 days, with no greater effects over time.

Two studies that addressed only sensory effects are summarized here (Astrand et al. 1972; Suzuki 1973). Experimental studies in controlled settings that evaluated neurotoxicity and subjective symptoms are summarized in Section 2.3 (Neurotoxicity), and a reproductive study that evaluated subjective symptoms (Luderer et al. 1999) is summarized in Section 2.4 (Developmental and

Reproductive Toxicity). All of these studies are summarized in Table 6-3, and are arranged in order of increasing concentration. Additional studies of controlled human exposures that evaluated the metabolism and disposition of toluene, but that did not address subjective symptoms, are summarized in Section 4.1 (Uptake, Metabolism, and Disposition).

Astrand et al. (1972) exposed 15 healthy male and female subjects, ages 18-46 year, to toluene at concentrations of 100 or 200 ppm for 30-min periods at rest and during exercise on a bicycle ergometer at work loads of 50 and 150 W. Some exposure periods were extended to 60 min at 100 ppm and 90 min at 200 ppm, the latter with exercise at 75 and 50 W for 30 min each. Toluene concentrations were measured by gas chromatography. No differences in measurements taken before or during exposure of heart rate, pulmonary ventilation, oxygen consumption, or blood lactate content for the corresponding workloads were found. Differences between males and females were minor. Although individual differences in uptake were noted, childhood asthma and obesity did not appear to affect uptake, and the presence of heart arrhythmias in two individuals, noted preexposure, was unaffected by the exposures. Exercise at 50 W in subjects exposed to toluene at 100 ppm more than doubled the subjects'arterial concentration of toluene (Astrand et al. 1972; Astrand 1975).

Suzuki (1973) exposed groups of five male students to toluene at 0 or 200 ppm for 6 h and measured several physiologic functions. The students reclined on a bed during the exposure. No significant changes were observed in galvanic skin reflex, vasoconstriction, respiration rate, or activity on electroencephalogram (EEG). Only heart rate was significantly increased (by 0.1 second) in the exposed group.

2.3. Neurotoxicity

The effects of toluene on nasal mucus flow, pulmonary function (nasal flow resistance, forced vital capacity, and forced expiratory volume), subjective response (headache and dizziness), and psychometric performance (both manual and mental tests) were evaluated several times during 6-h exposures to toluene at 10, 40, or 100 ppm (Andersen et al. 1983). The tests were carried out in an atmosphere-controlled chamber, and toluene concentrations were continuously monitored using gas chromatography and photo-ionization detection. Sixteen healthy male Danish students (average age 24), who were "nose breathers" volunteered for the study. Adaptation to the odor occurred, but odor was still noticeable at the higher concentrations at the end of the exposures. Three subjects reported that the odor/air quality at 100 ppm was unacceptable (not further explained). There was an increase in slight irritation of the eyes and nose, described as slight, and a reported decrease in air quality at 100 ppm as well as an increase in the perceived odor levels as test concentrations increased. The average

irritation score was 13 on a scale of 100, with one subject reporting a score of 64; six subjects reported no irritation during exposure at 100 ppm. No irritation of the throat or lower airways was reported at any concentration, and there was no effect on mood, fatigue, or sleepiness and no cough or nausea. However, an increase in the occurrence of headache, dizziness, and feeling of intoxication was found during the 100-ppm exposure; effects were described as slight to moderate and involved about half of the subjects (data were not presented). Pulmonary function and nasal mucus flow were unaffected by toluene inhalation. Furthermore, toluene had no significant effects on the performance of eight psychometric tasks measuring 20 different parameters, but there was a borderline significant decrease in three tests (multiplication errors, Landolt's rings, and the screw plate test) at 100 ppm.

Twelve healthy, adult men (ages 20-50) inhaled toluene at a constant concentration of 40 ppm for 4 h or were exposed to three 30-min peaks at 110 ppm over a 4-h period (Lammers et al. 2005a). Neurobehavioral tests were performed repeatedly during and after exposure. No effect on motor performance, attention, perceptual coding and memory, or mood was found with either exposure regimen. There were no further details in the available abstract.

In a study that evaluated acute symptoms and neurotoxicity manifest as sleepiness, Muttray et al. (2005) exposed 20 healthy male subjects to toluene at 0 or 50 ppm for 4.5 h. Toluene was monitored by infrared spectroscopy. Acute symptoms were assessed with a questionnaire, and sleepiness was assessed with the pupillographic sleepiness test, which measures changes in the diameter of the pupil of the eye. The subjects reported a bad smell and irritation of the throat during exposure at 50 ppm, but symptoms of headache, dizziness, nausea, tiredness, pain or pressure on the chest, coughing spells, shortness of breath, irritation of the eyes, watering eyes, blurred vision, irritation to the nose, running nose, an unpleasant taste, irritation to the skin, and feeling of fainting or vertigo were not significantly increased over control symptoms. Sleepiness was not increased.

Cherry et al. (1983) assessed the effects of a 4-h exposure to toluene at 80 ppm on four measures of performance and on mood. The subjects were eight male postgraduate students (ages 22-50), who were tested in groups of four in an atmosphere-controlled chamber. Test results of simple reaction time, four-choice reaction time, tracking task, and visual search were compared with those from a control group. Test results were also compared with those following exposure to alcohol (0.4 mL/kg) and following exposure to toluene and alcohol (0.4 mL/kg). In the control exposures, the chamber was primed with toluene to mask the control chamber. In both the control and exposure sessions, peppermint oil was used to mask the odor of toluene. The exposures were controlled by the investigators, but they took no part in the testing which was carried out blind. For the single exposures, the mean alcohol blood level was 49.9 mg%, and the mean blood toluene concentration was 12.7 mmol/L (both taken at the end of 4 h). Toluene

alone had no significant effect on any of the behavioral measures, whereas alcohol caused a significant deterioration on pursuit tracking, visual search tasks, and mood. Although the combination of toluene and alcohol had no significantly greater effect on any of the test results than alcohol alone, there was a nonsignificant tendency for performance and mood to deteriorate more than when alcohol was administered alone.

In a similar study, 16 healthy adult male volunteers, ages 23 to 38, were exposed to toluene at 0 or 80 ppm for 4 h in a controlled atmosphere chamber (Olson et al. 1985). Three different performance tests were administered: simple reaction time, choice reaction time, and memory. There were no differences in performance of tests involving simple reaction time, short-term memory, or choice reaction time immediately after entering the exposure chamber or after 2 or 4 h of exposure. On a rating scale of no, negligible, slight, and considerable, the subjects rated the discomfort (nausea, headache, or irritation in the eyes, nose, or esophagus) during the exposure as negligible.

The same investigators (Iregren et al. 1986) conducted another study in which they compared effects of toluene exposure to alcohol ingestion. Twelve men, ages 22-44 years, were exposed to toluene at 80 ppm toluene for 4.5 h. Results were compared with control exposures, exposure to toluene at 80 ppm accompanied by ingestion of alcohol (15 mmol/kg), and ingestion of alcohol alone. Neurobehavioral tests addressed choice reaction time, simple reaction time, color-word vigilance, and memory. The tests were administered prior to exposure and after 2 and 3.5 h of exposure. Symptoms and mood, including wakefulness, were also surveyed. Exposure to toluene at 80 ppm failed to affect performance on any of the tests, whereas the moderate ethanol intake resulted in gross performance changes in simple reaction time and color-word vigilance. There were no interactive effects of toluene and ethanol. Heart rate, EEG recordings, and sleep latencies were not affected by toluene treatment, although subjective symptoms of nausea, headache, and irritation were increased during the toluene and combined toluene and ethanol exposures. However, mood symptoms (feeling bored, sleepy, or irritated) were not different between the exposed and control groups. The subjective symptoms were the same as those reported in the earlier study of Olson et al. (1985), which were rated in that study as negligible in the control and exposed groups.

Winneke (1982) exposed 18 subjects to either air or toluene at 100 ppm in a controlled chamber for a 3.5 h period. Critical flicker frequency (the illusion of motion due to persistent sensory neuron excitation after a stimulus has ended) was measured as a perceptual measure of CNS activation. Sustained attention was measured with a bisensory vigilance task. At the end of the exposure, a comprehensive battery of psychomotor tests (not defined) was administered. None of the measures showed a significant effect from toluene exposure.

Dick et al. (1984) exposed 30 male and female subjects to toluene at 100 ppm for 4 h. Subjects were exposed to either a placebo (a 2-min exposure to

toluene at 25 ppm followed by air) or toluene at a concentration of 100 ppm in an atmosphere-controlled chamber. Solvent concentration was monitored using an infrared analyzer and analysis was carried out by gas chromatography every 3 min. Compared with the control values, toluene exposure did not adversely affect the outcomes on 27 psychomotor tests. A slight, but statistically significant, decrement was observed on the visual-vigilance test; the percentage of correct hits was lower. The authors considered the overall results to demonstrate a failure to induce cognitive effects.

A double-blind study by Rahill et al. (1996) tested toluene at 100 ppm or air only for 6 h. Six healthy male and female subjects, ages 27-38, performed complex psychometric and response-time tasks during rest and following exercise sessions sufficient to quadruple the resting ventilation rate. Pulmonary function tests, consisting of forced vital capacity and forced expiratory volume in 1 second (sec), were also carried out prior to and after the exposure. The subjects filled out a 56-item questionnaire concerning symptoms and mood before and after the exposure. Each subject served as his or her own control. The exposures were carried out in a large atmosphere-controlled chamber, and the toluene concentration was monitored by an infrared analyzer. Latency but not accuracy during neuropsychologic tests proved sensitive to toluene. The latency was greatest following the exercise period. The composite score obtained over time during toluene exposure was lower than that during the air exposure. However, the differences between the air- and toluene-exposed groups, while in some cases statistically significant, were characterized by the study authors as subtle. For example, the composite score for an hour-long multitasking test was reduced by 11% following the toluene exposure compared with control score. Pulmonary function was not affected by toluene exposure in this study. No subjective symptoms were reported, and mood was only slightly changed. The mood change was characterized as a "reduced positive mood." This experiment demonstrated that physical activity can exacerbate the response to toluene as greater, but subtle, differences in performance were observed after exercise.

Baelum et al. (1985) reported that the acute effects of toluene exposure are slightly more pronounced for previously exposed workers (rotogravure printers) compared with previously unexposed controls. The printers had been exposed to solvents for 9-25 years. Male subjects (43 printers and 43 controls), ages 29-50 years, were divided into four matched groups (20 control printers, 19 tolueneexposed printers, 21 unexposed controls, and 15 toluene-exposed controls) and exposed to either air (20 control printers and 21 controls) or toluene at 100 ppm (19 printers and 15 controls) for 6.5 h, preceded by a 1-h acclimatization period. Subjective evaluations concerning the quality of the environment were taken before exposure and at 0.5 and 6.5 h. Nine visuomotor-coordination and perceptual-speed tests were administered at several hours into the exposure. A colordiscrimination test was administered before and during exposure. The effects observed at 100 ppm for both exposed groups compared with control groups

included discomfort with complaints of low air quality, strong odor, fatigue, sleepiness, a feeling of intoxication, and irritation of the eyes, nose, and throat. However, complaints increased for all subjects during the test periods (including the controls) and neither annoyance nor nausea was experienced. Tolueneexposed printers were slightly slower than nonexposed printers on one of six manual dexterity tests ($p < 0.05$), but toluene-exposed controls and nonexposed controls had similar results on this test. The same relationship was found for one visuomotor test (Landolt's rings); more errors were made by exposed printers compared with unexposed printers and no differences were found between exposed and unexposed control groups. Both groups of printers made fewer errors on a color-discrimination test administered before exposure compared with both groups of controls, but the error rate decreased later in the exposure for both groups of controls, whereas there was almost no improvement for either of the toluene-exposed groups. Although no significant differences were observed between the occupationally-exposed group and the naive subjects, the authors stated that there was a tendency toward greater sensitivity among occupationallyexposed subjects.

As part of the same study, Nielsen et al. (1985) evaluated the renal function of the printers and control groups. Urinary samples were taken before the exposure, at 3 h after the start of exposure, and again at 6 h after the start of exposure. No significant changes in β-microglobulin- or albumin-excretion rates were observed for the exposed subjects compared with the air controls. The authors concluded that there is no causal relationship between moderate exposure to organic solvents and renal injury.

Stewart et al. (1975) exposed 10 male subjects to toluene at 0, 20, 50, or 100 ppm and nine female subjects at 100 ppm for 1, 3, or 7.5 h over several days. The exposures at 100 ppm were for five consecutive days. Males were also exposed to a fluctuating concentration of 50-150 ppm (mean concentration 100 ppm) for 1, 3, or 7.5 h for 2 days. Ages ranged from 19-47 years old. Subjects were exposed at each concentration in groups of two to four, with never more than eight subjects in the chamber at one time (subjects exposed for 1 h exited the chamber after 1 h and the subjects exposed for the longer durations remained). Male subjects exercised for 5-6 min once during the shorter exposures and twice during the 7.5-h exposure. Chamber atmospheres were monitored with gas chromatography and infrared spectroscopy. Each subject was given a complete medical examination before and after exposure; additional evaluations included hematology and clinical chemistry parameters, EEG recordings (with an amplified visual evoked response), pulmonary-function tests, heart rate, equilibrium tests (modified Romberg), and cognitive tests. Subjective symptoms were also evaluated. Not all evaluations took place every day or with all subjects. There was no decrement in several psychomotor performance tests, except for females exposed at 100 ppm for 7.5 h on the second day. They had fewer correct responses on a dual task involving visual vigilance and tone detection on the second and fifth days of

exposure. This decrement was not observed in male subjects or in females during the 3-h exposure. Performance on time estimation, addition, and coordination tests did not change. On the fifth day of exposure at 100 ppm for 7.5 h and during the fluctuating exposure at 100 ppm, one of two male subjects had a slight increase and decrease, respectively, in the visual evoked potential. This change was not observed in female subjects. When toluene was present in the chamber, all subjects noticed a mild to strong odor when entering the chamber; adaptation occurred for most subjects. There was no increase in drowsiness, fatigue, sleepiness, or headache or change in appetite or sleep habits. Subjective complaints of irritation were greater during the 3-h exposure at 100 ppm than during the 1- or 7.5-h exposure at 100 ppm. Types and incidences of subjective complaints were similar between controls and the exposed subjects during the 7.5-h exposure at 100 ppm.

An evaluation of human responses to varying concentrations of toluene with a TWA of 100 ppm (with peaks at 300 ppm every 30 min) was conducted by Baelum et al. (1990). The authors compared the symptoms during the varying concentrations to those during exposure to a constant concentration of toluene at 100 ppm and to those reported in a clean air control. Thirty-two males and 39 females comprised a random sample of the population between the ages of 31 and 50. The subjects were healthy males and females who did not abuse alcohol or drugs and were able to exercise for 15-min periods with a load of 50, 75, or 100 W during the peak exposures. The clean air, constant exposure, and varying exposure groups comprised 23-24 subjects each. Exposures were carried out for 7 h, and concentrations were measured using a flame ionization detector. Both toluene-exposed groups complained significantly more about the poor air quality, altered temperature perception, feeling of intoxication, and increased irritation in the nose and lower airways (but not of the eyes); there was a tendency toward an increase in dizziness and feeling of intoxication in the exposed groups (controls reported scores similar to those of the constant exposure-group for fatigue, sleepiness, and headache). There was a tendency toward lower scores on vigilance tests for the toluene-exposed groups compared with the control, indicating only a minimal effect on psychomotor performance, as scores on other assessment tests were normal. There was not, however, a significant difference between symptoms or performance between the two toluene-exposed groups.

Echeverria et al. (1989, 1991) reported on the acute neurobehavioral effects of toluene in tests with 42 healthy male and female college students. The toluene concentrations tested were 0, 75, and 150 ppm over a 3-day period (7 h each day) and were administered in random order. The odor of toluene was masked with menthol (0.078 ppm). Chamber atmospheres were measured with an infrared analyzer and confirmed by gas chromatography. A battery of 12 performance tests (verbal, visual, and psychomotor) was administered to each participant before the exposures and again at 4 and 7 h during the exposures. Test results were averaged over the 3 days. The initial test results served as control values. A mood and fatigue checklist was also incorporated into the protocol. A 5-12% decrement in

performance was considered significant if consistent with a linear trend. The results of this study included a significant decrement in performance on several tasks when subjects were exposed to toluene at 150 ppm; they included losses of 6.0% for digit span, 12.1 % for pattern recognition (increase in latency of 0.3 sec), 5.0% for pattern memory (number correct), 6.5% for one hole, and 3% for critical tracking. These differences, although statistically significant, were small. Although the pattern of moods scale and fatigue symptoms were not affected by toluene, the frequency of headaches and ocular irritation increased slightly in a concentration-dependent manner, as did the number of observations of sleep during exposure. For example, headache was reported by 8, 11, and 14% of individuals exposed at 0, 75, and 150 ppm, respectively. Sleep did not confound the behavioral scores. The reports of ocular irritation and headache were greatest on the first day of exposure.

Ogata et al. (1970) measured the effects of exposure to toluene at 100 or 200 ppm on blood pressure, pulse rate, flicker value (not defined), and eye-tohand reaction time in 23 male students. Subjects were exposed for 3 h in the morning and 4 h in the afternoon, the latter following a 1-h break. After a 3-h exposure at 200 ppm, the mean pulse rate was decreased significantly compared with a control group. However, there was no dose-response relationship and all pulse rates were lowered as exposures continued. The authors stated that there was a tendency for reaction time to be prolonged during the 200-ppm exposure, but there was no clear concentration-response relationship.

Twelve healthy male subjects, ages 20 to 35, were exposed to successively increasing concentrations of toluene at 100, 300, 500, and 700 ppm, for four successive 20-min periods (Gamberale and Hultengren 1972). There was a 5min break between the exposure at 300 ppm and at 500 ppm. The air-toluene mixture was administered via a breathing valve and a mouthpiece to the sedentary subjects. The odor of toluene was masked with menthol-crystals, and only one of the 12 subjects was able to correctly distinguish between conditions with and without toluene. Four performance tests were administered during the last 15 min of each exposure: two perceptual speed tests, simple reaction time, and choice reaction time. Test results were compared with results during air exposures. An increase in simple reaction time (to a stimulus) was observed at 300 ppm (controls, 222 msec; 300 ppm, 236 msec), complex reaction time was affected at 500 ppm, and a decrease in perceptual speed occurred at 700 ppm. The decrease in perceptual speed was relative to the control values, which decreased with each successive exposure (learning effect); speed also decreased for the exposed group but not as rapidly as for the control group. The authors stated that short-term exposures to toluene below 300 ppm are not associated with psychomotor dysfunction. Heart rate declined during the 85-min test period in accordance with increasing familiarity with the test situation and individual test and was little affected by toluene exposure.

Carpenter et al. (1976) reported several human and animal responses to "Toluene Concentrate," a hydrocarbon mixture produced by a large solvent manufacturer in the United States. This mixture contained toluene (45.89 %), butanes, pentanes, hexanes, heptanes, octanes, cyclopentanes, cyclohexanes, and benzene. Gas-chromatographic analysis was used to monitor exposure concentrations. Six of six subjects indicated they would be willing to work an 8-h day while being exposed to toluene concentrate at 480 ppm (220 ppm of toluene), a concentration at which some ocular irritation was reported after a 15-min exposure. Three of these six people reported that they would be willing to work an 8-h shift while being exposed to toluene concentrate at 930 ppm (427 ppm of toluene).

Horvath et al. (1981) exposed a group of 11 male volunteers, ages 20-21, to three 70-min sessions of toluene at 240 ppm, during which the subjects performed a vigilance task. The task consisted of spatial discrimination of low frequency acoustical clicks, which contributed to the monotony of the task, and a concurrent visual feedback task. The toluene concentration was increased gradually over the test period, reaching and maintaining a maximum concentration of 240 ppm over the last 30 min of each session. There was a 70-min period between exposures. For comparison purposes, additional subjects ingested 5 or 10 mg of diazepam, a known psychotropic drug, or were exposed to a combination of toluene and diazepam (5 mg). There were no effects from exposure to either toluene or diazepam on vigilance during the first session, and there was no effect of toluene on vigilance during the second session, although vigilance errors were increased in the groups that had ingested diazepam (both doses) and in the group exposed to both toluene and diazepam. During the third session, vigilance errors were increased for all groups except the control group. Errors were highest in the groups exposed to 10 mg of diazepam and both diazepam and toluene. The authors considered the effect an impaired alertness. The subjective symptom survey found decreased fatigue and sleepiness, especially during the second session.

Two older studies are reported here for completeness of the data base (von Oettingen et al. 1942; Carpenter et al. 1944). These studies used outdated analytic techniques and a small number of subjects compared, and are not included in Table 6-3. von Oettingen et al. (1942) conducted a study with three healthy human volunteers, ages 35 to 53; toluene concentrations were controlled and measured by interferometric determinations. Subjects were exposed at 0, 50, 100, 200, 300, 400, or 600 ppm for 8-h sessions (with a 30-min break) over the course of an 8-week period (each exposure was separated by several days). Two of the subjects were also exposed at 800 ppm for 3 h, then for another 2 h following a 2-h break. Many of the exposures were repeated, with a break of several days between exposures. Blood pressure, pulse rate, respiratory rate and volume, differential blood cell count, and clinical chemistry parameters were monitored. Subjective symptoms were also evaluated. There were no effects of exposure on cardiac or respiratory parameters or hematology or clinical chemistry parameters at

concentrations up to 500 ppm. Decreased erythrocyte count was observed at 800 ppm. At 50 ppm, one of two subjects had no subjective complaints and the other complained of very mild headache and drowsiness (subjects also complained of moderate tiredness toward the end of the control exposure). At 100 ppm, moderate fatigue and sleepiness were the only complaints. Acute exposure to toluene at a concentration of 200 ppm for 8 h produced headache, nausea, muscular weakness, confusion, impaired coordination, and dilated pupils, as well as after-effects including fatigue, general confusion, and moderate insomnia in one, two, or all of the subjects. Higher concentrations produced effects similar to the 200-ppm exposure; however, the effects were more pronounced and the after-effects were prolonged. Olfactory adaptation to the odor was rapid, and other than a slight smarting of the eyes and nose, none of the exposures produced irritation of the mucous membranes.

Carpenter et al. (1944) exposed two subjects to toluene at 200, 400, 600, or 800 ppm for 7-8 h. Subjective symptoms ranged from transitory mild throat and ocular irritation and slight exhilaration at 200 ppm to metallic taste, transitory headache, extreme lassitude, scotomata, verbosity, inebriation, and slight nausea at 800 ppm. After the initial exposure, some adaptation to the subjective symptoms occurred. The threshold for inability to perform a steadiness task (holding a wire in a 0.25-in hole without touching the sides) was 800 ppm. Toluene was evaporated from a heated dish; vapor concentrations were measured with an interferometer.

In order to simulate an abuse situation, a researcher inhaled toluene from a paper bag containing gauze soaked with toluene (Press and Done 1967). The exposure consisted of "rapid, deep inhalations and exhalations directly into a brown paper bag containing the contents of two tubes of 3/4 oz each of Testor's cement...". The estimated concentration of toluene in the paper bag was 10,000 ppm (3.6 mg of toluene/100 mL of air). During the 5-min exposure, the subject had sensations of dizziness, blurred vision, roaring and buzzing in the ears, and slurred speech. An electroencephalogram taken during the exposure was normal. "Blood levels exceeding 1.75 mg/100 mL were reached." Because the concentration was estimated, this study is not included in Table 6-3.

2.4. Developmental and Reproductive Toxicity

Reproductive and developmental toxicity of toluene have been reviewed by Donald et al. (1991) and ATSDR (2000). Data regarding human developmental and reproductive toxicity are restricted to chronic exposures and include only continuous occupational or abuse situations. Intrauterine growth retardation, spontaneous abortion, premature delivery, congenital malformations, and postnatal developmental delays are clearly associated with gross toluene exposure; maternal toxicity at very high abuse concentrations includes overt CNS

depression, renal tubular acidosis, and fatty liver. Further confounding these report are social and health status variables, as well as the possibility of exposure to other fetotoxic agents (either as impurities or admixtures in toluene-containing products) or deliberate or accidental exposures to other chemicals or drugs (especially ethanol), which are not accounted for in these reports. These studies provide little quantitative information regarding dose response and are not considered in the development of AEGL values.

Luderer et al. (1999) examined the reproductive endocrine effects of acute exposure on males and females. Women were divided into two groups comprised of those in the follicular phase and those in the luteal phase of the menstrual cycle. Groups consisted of four or five individuals with a similar number of matched controls. A 3-h exposure at 50 ppm via a mouthpiece did not result in alterations of the serum gonadotrophins comprising luteinizing hormone and follicle-stimulating hormone; however, subtle effects on luteinizing-hormone secretion in men and women, the latter in the luteal phase, were found. There was no effect on blood testosterone concentrations in men. The authors stated that the clinical relevance of the subtle effects on luteinizing-hormone secretion is unclear.

Gericke et al. (2001) found no effect of chronic toluene exposure on follicle-stimulating hormone, luteinizing hormone, or testosterone of 1,077 male subjects compared with a referent group. There is some indication that lower concentrations of hormones, follicle-stimulating hormone, luteinizing hormone, and serum testosterone (Svensson et al. 1992) and dysmenorrhea (Ng et al. 1992) may be associated with occupational exposure to toluene. However, Ng et al. (1992) state that it is uncertain whether other behavioral and work-related factors may also have contributed to the incidence of dysmenorrhea.

2.5. Genotoxicity

Several investigators examined the effect of occupational exposures to toluene on peripheral lymphocytes. Chromosome analyses of 24 workers (Forni et al. 1971) and 32 workers (Maki-Paakkanen et al. 1980) at rotogravure plants revealed no significant differences in the frequencies of sister chromatid exchanges (SCEs) or chromosomal aberrations between the workers and matched controls. Bauchinger et al. (1982) examined peripheral lymphocytes in a group of male rotogravure workers who were occupationally exposed only to toluene for more than 16 years. The ages ranged from 32 to 60; 11 workers were heavy smokers (more than 10 cigarettes per day). A similar number of smokers (eight of 24) comprised the control group. Subjective complaints were similar among both groups and there was no evidence of neurologic damage in either group. The rotogravure workers had significantly more chromatid breaks, chromatid exchanges, and gaps than the control group. The continuously measured toluene concentration in the work room was between 200 and 300 ppm (benzene was <0.3%). Hammer (2002) found a three-fold increase in SCEs in 42 rotogravure

printing plant workers exposed to toluene at 38-88 ppm compared with a control group. Ambient air and blood toluene concentrations did not show a relationship to SCEs, but there was a significant relationship with cresol metabolites in the urine.

Five adult male volunteers were exposed to toluene at a concentration of 50 ppm for 7 h/day for 3 days; this exposure regimen was repeated three times over 2 weeks (Richer et al. 1993). Peripheral blood lymphocytes were evaluated for SCEs, cell-cycle delay, and cell mortality. Although cell mortality was temporarily increased, disappearing after 15 h, there were no changes in cytogenetic parameters.

An in vitro experiment conducted by Gerner-Smidt and Friedrich (1978) showed that toluene concentrations up to of 1.52 mg/mL failed to alter the number of SCEs or the number of chromosomal aberrations in human lymphocytes compared with controls. In this study, toluene at 1,520 ppm did, however, produce significant cell-growth inhibition compared with controls.

2.6. Carcinogenicity

An epidemiologic study by Carpenter et al. (1988) compared deaths from cancers of the CNS in workers at the Y-12 nuclear facility or Oak Ridge National Laboratory (Oak Ridge, TN) with a group of controls. The workers had been exposed for a mean period of 5 years to solvents (toluene, xylene, and methyl ethyl ketone). No increased incidence in death from cancers of the CNS was found compared with controls. No estimation of exposure concentrations was made in this study.

Another study of occupational exposure to toluene was conducted involving 1,020 rotogravure printers exposed to toluene who were employed for a minimum of 3 months between 1925 and 1985 (Svensson et al. 1990). Estimated concentrations of toluene ranged from 450 ppm in the 1940s to as low as 30 ppm by the mid-1980s; workers were also exposed to various concentrations of benzene and other hydrocarbons for various durations. When the data were analyzed for workers who had been exposed for at least 5 years and a latency of 10 years, no significant increase in deaths from cancers was observed.

The International Agency for Research on Cancer (IARC 1999) has assessed the carcinogenicity of toluene. Its evaluation states that there is *inadequate evidence* in humans and *evidence suggesting lack of carcinogenicity* of toluene in experimental animals. IARC (1999) concluded that "toluene is *not classifiable as to its carcinogenicity to humans (Group 3)*." EPA (2007) has not classified toluene as to its carcinogenicity because there are no human data and animal data are inadequate.

2.7. Summary

Toluene is relatively nontoxic (NRC 1981). Effects of acute exposures are limited to CNS depression, cardiac arrhythmias, and renal toxicity (NRC 1981). Even concentrations that produced unconsciousness failed to produce residual organ damage. Deaths have been reported following exposure at "high concentrations" of toluene and are usually associated with intentional solvent abuse. The "high concentrations" in these abuse situations can seriously inhibit CNS function and predispose subjects to cardiac arrhythmias. Severe renal tubular acidosis has been described in several abuse situations and in some accidental exposures. Effects on the blood and bone marrow were observed during some early studies, when industrial toluene was contaminated with benzene or used in conjunction with benzene (von Oettingen et al. 1942; Massengale et al. 1963), a known bone marrow suppressant. The highest non-fatal vapor exposures occurred during accidental exposures and the concentrations were either calculated or measured after the exposure. Concentrations of greater than 5,000 ppm for an undefined time (Longley et al. 1967) and greater than 1,842 ppm for several hours (Meulenbelt et al. 1990) resulted in unconsciousness and disorientation, respectively. Recovery was complete in both cases.

Toluene is not a primary irritant. Slight irritation of the eyes and nose has been reported in several controlled clinical studies during 6- to 8-h exposures to at 100 ppm or higher (Carpenter et al. 1944; Andersen et al. 1983; Baelum et al. 1985, 1990; Echeverria et al. 1989), but there was no annoyance or discomfort associated with the exposures (Baelum et al. 1985). Furthermore, irritation was not among the reported symptoms during exposures of up to 800 ppm (von Oettingen et al. 1942) or in many occupational monitoring studies where concentrations were 100 ppm or higher (Greenberg et al. 1942; Wilson 1943; Foo et al. 1990; Ukai et al. 1993; Neubert et al. 2001a). No dermal, ocular, or throat irritation was reported in painters exposed to toluene at 1,100 ppm (Greenberg et al. 1942) or in accident situations where concentrations may have been greater than 5,000 ppm (Longley et al. 1967). Adaptation occurs to the odor (Stewart et al. 1975; Andersen et al. 1983; Mergler and Beauvais 1992) and potential drying effects on the mucous membranes (Carpenter et al. 1944; Andersen et al. 1983).

The primary effect associated with inhalation exposure to toluene is CNS depression. Fifteen of the approximately 20 studies in Table 6-3 addressed neurobehavioral effects. The neurobehavioral end points in these studies measure very subtle changes in reaction time and cognitive ability. The concentration of 100 ppm was a no-effect level for most neurobehavioral end points, including vigilance and reaction time (Ogata et al. 1970; Gamberale and Hultengren 1972; Stewart et al. 1975; Winneke 1982; Andersen et al. 1983; Dick et al. 1984; Baelum et al. 1990; Rahill et al. 1996). The effect of exercise, which results in increased uptake of toluene, was evaluated in the studies by Baelum et al. (1990) and Rahill et al. (1996). No gross neurobehavioral deficits were observed at 150 ppm (Echeverria et al. 1989), 200 ppm (Ogata et al. 1970), or 100 ppm with peaks to

300 ppm with an exercise protocol (Baelum et al. 1990). No greater effects were observed when exposures were repeated over several days (Stewart et al. 1975; Echeverria et al. 1989), and no significant gender differences were observed (Stewart et al. 1975). No impairment in alertness occurred during two successive 70-min exposures to toluene at 240 ppm (Horvath et al. 1981), although the results of the study were difficult to interpret. A significant increase in time to complete a complicated task involving perceptual speed (45.5 vs 36.9 sec) was observed at 700 ppm, following 20-min exposures at lower concentrations (Gamberale and Hultengren 1972). The studies by von Oettingen et al. (1942) and Carpenter et al. (1944) were reported for completeness of the data base, but were not considered in development of AEGL values because of the impurity of the toluene, the less accurate analytic measurement methods (inferometrics is no longer an acceptable analytic method and the reliability of the combustible gas indicator is lower than the range measured), and the small number of subjects compared with later studies.

Developmental toxicity data from animal studies show that the developing embryo is no more sensitive to the toxic effects of toluene exposure than is the mother (ACGIH 2005). Developmental delay and congenital malformations resembling those of fetal alcohol syndrome have been observed in pregnant women after intentional inhalation of concentrated toluene vapor. These conditions were the result of chronic toluene abuse during pregnancy. There is no evidence that this syndrome occurs in women who are exposed occupationally to toluene.

The relationship of toluene exposure to mutagenicity and genotoxicity is unclear as conflicting results were observed in several studies. Examination of peripheral lymphocytes of clinically-exposed volunteers and occupationallyexposed workers were generally negative for chromosome aberrations and SCEs, but were positive or questionable in other studies (Bauchinger et al. 1982; Hammer 2002). The human data are insufficient for cancer classification of toluene exposure in humans at this time, but examinations have found no association between cumulative toluene dose (as ppm-years) and standardized mortality ratios for either all sites or for respiratory tract cancers (Svensson et al. 1990).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Acute lethality data were available for the rat and mouse, and lethal concentration data from these studies are summarized in Table 6-4. Additional data from studies with the dog, cat, and rabbit were available but provide little information on the threshold for lethality.

3.1.1. Dogs

Ikeda et al. (1990) examined the cardiovascular response in 25 dogs during acute inhalation of toluene at 30,000 ppm for 9-10 min. Electrocardiograms revealed no changes for the first 3-4 min of exposure; tachycardia ensued for several minutes and was followed by a period of bradycardia. In some dogs, ventricular fibrillation ensued shortly thereafter, followed by death. Kobayashi et al. (1989) reported that the threshold concentration of toluene for decreasing left-ventricle contractility in dogs was 3,800 ppm.

3.1.2. Rats

Pryor et al. (1978) exposed groups of male Fischer rats to various undefined concentrations of toluene. All rats died during a 1-h exposure at 40,000 ppm. The 1-h LC_{50} (lethal concentration, 50% lethality) was 26,700 ppm.

Cameron et al. (1938) in a summary of their earlier work reported that the 6.5-h LC_{50} for Wistar rats was approximately 12,200 ppm. Mortality was 60% during a 1.5 h exposure at 24,400 ppm and all 10 rats died when this exposure was extended to 6 h. No rats died during a 24-h exposure to toluene at 6,100 ppm. Nine-day old rats were more resistant to toluene than adult rats. Rats survived fourteen 8-h exposures at 1,525 ppm. No details of the exposures were provided. Smyth et al. (1969) reported that one of six rats exposed at 4,000 ppm for 4 h died. No further details were provided in this range-finding study, and the study is not reported in Table 6-4.

In a study by Shell Oil Company (1982), groups of three male and three female Wistar rats inhaled measured concentrations of toluene at 18,100-18,800 ppm for up to 7 h. All rats survived the 3-min exposure. After exposures at 18,100 ppm for 1 min, 18,500 ppm for 30 min, and 18,900 ppm for 7 h, mortality was 17, 83, and 100%, respectively. At all concentrations, signs during exposure included agitation, salivation, and ocular and nasal discharge. Except for the 3-min exposure, rats became comatose, usually with whole-body tremors. Animals gained consciousness 1h after exposure. DuPont Chemical Company (1966) reported a 4-h LC_{50} of 18,300 ppm for male CD rats.

TABLE 6-4 Summary of Acute Lethal and Sublethal Toxicity of Toluene in Laboratory Animals

Species	Concentration (ppm)	Exposure Duration	Effects	Reference
Dog	30,000	10 min	Successive tachycardia, bradycardia, and ventricular fibrillation, followed by death.	Ikeda et al. 1990
Rat	26,700	1 h	LC_{50}	Pryor et al. 1978
	40,000	1 h	100% mortality	
Rat	24,400 24,400	6 h	100% mortality	Cameron et al. 1938
	12,200	1.5 h	60% mortality	
	6100	6.5 h	50% mortality No	
		24 h	deaths	
Rat	20,000 15,000	50 min	100% mortality	Kojima and Kobayashi 1973
	12,200	2.5 h	80% mortality	
	10,000	2-2.5 h	LC_{50}	
	5,000	2 h	20% mortality No	
		2 h	deaths	
Rat	18,900 18,500	7 h	100% mortality	Shell Oil Company 1982
	18,100	30 min	83% mortality	
	18,500	10 min	17% mortality	
		3 min	No deaths	
Rat	18,300	4 h	LC_{50}	DuPont Company 1966
Rat	15,000	1 h	No deaths	Hinman 1987
Rat	6,000	4 h	No deaths	Wada et al. 1989
	7,670	4 h	25% mortality	
Rat	6,250	2 h	No deaths	Mullin and Krivanek 1982
	3,100	4 h	No deaths	
Rat	2,667	7.5 h	No deaths	Lammers et al. 2005b

(Continued)

TABLE 6-4 Continued

Species	Concentration (ppm)	Exposure Duration	Effects	Reference
Mouse	38,465 21,872 19,018 6,000[a]	10 min 30 min 60 min 30 min	LC_{50} LC_{50} LC_{50} No deaths	Moser and Balster 1981; 1985
Mouse	24,400 24,400 12,200 6,100	6 h 1.5 h 6.5 h 24 h	100% mortality 10% mortality 100% mortality No deaths	Cameron et al. 1938
Mouse	12,000 8,600 4,000	20 min 3 h 3 h	No deaths LC_{50} No deaths	Bruckner and Peterson 1981a,b
Mouse	10,000	1 h	No deaths	Bushnell et al. 1985
Mouse	6,940	6 h	LC_{50}	Bonnet et al. 1979
Mouse	5,320	7 h	LC_{50}	Svirbely et al. 1943

[a] Exposures were repeated for 7 weeks.

Kojima and Kobayashi (1973) exposed groups of five male albino rats to concentrations of toluene ranging from 5,000 to 25,000 ppm for 2 to 2.5 h. No rats died following exposure at 5,000 ppm for 2 h. One of five rats died during a 2-h exposure at 10,000 ppm. Four of five rats died during a 2.5-h exposure at 15,000 ppm. All rats exposed at 20,000 ppm died within 50 min. Death was attributed to CNS depression.

As part of a neurotoxicity study (see Section 3.3.2), Mullin and Krivanek (1982) exposed groups of six male CD rats to measured concentrations of toluene at 810, 1,660, and 3,100 ppm for 4 h and at 6,250 ppm for 2 h. No deaths were reported following exposures to toluene, whereas deaths were reported in similar tests with other chemicals. In other neurotoxicity tests described in Section 3.3, no deaths occurred in adult male Long-Evans rats exposed to toluene at 15,000 ppm for 1 h (Hinman 1987) or in male WAG/RijCrlBR rats exposed at 2,667 ppm for 7.5 h (Lammers et al. 2005b). No deaths occurred in adult male Wistar rats exposed at 6,000 ppm for 4 h, but two of eight rats exposed at 7,670 ppm for 4 h died (Wada et al. 1989). The fact that some of these animals were performing learned tasks increased the rate of uptake of toluene.

3.1.3. Mice

Moser and Balster (1985) exposed groups of 12 male CD-1-mice to several undefined toluene concentrations for 10, 30, or 60 min. Animals were examined for lethality and behavioral toxicity (inverted screen test). The LC_{50} values for the 10-, 30-, and 60-min durations were 38,465 ppm (confidence limit: 36,067-41,023 ppm), 21,872 ppm (confidence limit: 20,731-23,076 ppm), and 19,018 ppm (confidence limit: 17,350-20,846 ppm), respectively. The authors noted that as solvent concentrations were increased for the lethality studies, mice displayed a progression of clinical signs from excitability and hyperactivity to lethargy and hypoactivity. Shallow, rapid respiration ensued and was followed by death within 1 h after the exposure. All mice survived repeated exposure at 6,000 ppm for 30 min/day, 5 days/week for 7 weeks and appeared in good health (Moser and Balster 1981).

Cameron et al. (1938) exposed groups of 10 mice (strain not specified) to concentrations of toluene at 6,100-24,400 ppm for various durations. Mortalities were 10% and 100% following 1.5- and 6-h exposures, respectively, at 24,400 ppm. Mortality was also 100% after a 6.5-h exposure at 12,200 ppm. All mice survived a 24-h exposure at 6,100 ppm. No further details of the exposures were given.

As part of a study on the pharmacology and pharmacodynamics of toluene, Bruckner and Peterson (1981a) exposed groups of up to 14 male ICR mice to toluene at concentrations ranging from 2,600 to 12,000 ppm. The 3-h LC_{50} was 8,600 ppm (95% confidence interval: 8,000-9,200 ppm). No further details were

provided. In a companion paper, no deaths were reported in mice exposed at 4,000 ppm for 3 h/day, 5 times weekly for 8 weeks (Bruckner and Peterson et al. 1981b). Similarly, no deaths were reported in adult C57BL/6J male mice

exposed at 10,000 ppm for approximately 1 h or in mice exposed at 3,000 ppm for 5 h/day for 90 days (Bushnell et al. 1985). In a study by Bonnet et al. (1979), the 6-h LC_{50} was 6,940 in mice. No further details were available.

Acute toxicity studies in Swiss mice conducted by Svirbely et al. (1943) revealed progressive symptoms prior to death, including restlessness, muscular twitching, an S-shaped curve in the tail, dyspnea, incoordination, and evidence of a narcotic effect. Toluene concentrations ranged from 3,660-8,520 ppm, as measured by a refractometer. The 7-h LC_{50} was 5,320 ppm (confidence limits: 4,960 and 5,710 ppm). Microscopic examination of the major organs failed to identify lesions with the exception of casts and debris in the renal tubules of some mice.

3.2. Nonlethal Toxicity

3.2.1. Dogs

von Oettingen et al. (1942) exposed six dogs to toluene at 850 ppm for 1 h. This exposure resulted in an increase in respiratory rate and a decrease in respiratory volume. No further details were provided.

3.2.2. Rats

Most studies of acute exposures of rats to sublethal concentrations of toluene evaluated neurotoxicity and are summarized in Section 3.3.2. Subacute exposures to toluene have produced hearing loss in rats. Hearing loss was found in young rats after exposure to toluene at 2,000 ppm for 8 h/day for 3 days or at 1,500 ppm for 14 h (Pryor et al. 1984). Permanent loss of hearing in the high frequency range was found when young rats were exposed at 1,200 ppm for 14 h/day, 7 days/week for 5 weeks. Morphologic examinations revealed loss of, or damage to, hair cells in the basal turn of the cochlea.

Toluene was also tested for its influence on ventricular arrhythmias in the rat. Previous inhalation of toluene by Wistar rats, at up to 7,387 ppm for 15 min, reduced the ectopic ventricular activity caused by coronary ligation or administration of aconitine (Magos et al. 1990). These results contrast with those with benzene, in which arrhythmias were increased in the 30 min following induction of arrhythmia. Following a near-lethal exposure to toluene at 66,000 ppm for 30 min, injection of epinephrine did not induce arrhythmia or ectopic beats in anesthetized rats (Vidrio et al. 1986).

3.2.3. Mice

Exposure of eight male ICR mice to toluene at 4,000 ppm for 3 h resulted in elevated blood SGOT 24 h after (Bruckner and Peterson 1981b). Repeated exposures for 3 and 5 days also resulted in elevated SGOT, with the increase significant after the 1- and 3-day exposures. When the exposures were extended to five times

weekly for 8 weeks, transient body weight depression and increased hepatic weights were observed. Histopathologic findings in the heart, lungs, kidneys, brain, and liver were generally unremarkable.

The sensory irritation response in groups of four male Swiss-Webster mice during a 30-min exposure at several concentrations of toluene (900, 1,700, 2,600, 3,500, 4,100, 5,050, 6,400, or 7,800 ppm) was evaluated by Nielsen and Alarie (1982). From these data, the RD_{50}, the concentration that depresses the respiratory rate by 50%, was calculated. At 900 ppm, there was no effect on the respiratory rate. Toluene concentrations of 2,600 ppm and higher produced a rapid, brief (approximately 1 min) decrease in the respiratory rate, followed by an increase above the control level within the next 6 min (stimulatory effect). At 7,800 ppm, the initial depressive effect on the respiratory rate was modified by the stimulatory effect at this concentration; after the brief depression, the increased respiratory rate, up to 140% of the control value, was sustained over the 30-min exposure. The RD_{50}, calculated on the basis of the initial depression, was 5,300 ppm. In cannulated mice, only a small decrease in respiratory rate occurred at the beginning of exposures, even at the higher concentrations. The authors discuss the fading of the sensory-irritation response or desensitization that occurs with some chemicals including some alkylbenzenes, making measurement of an RD_{50} difficult. The stimulatory effect was attributed to systemic absorption of toluene from the lung. In a similar study and using OF_1 mice, De Ceaurriz et al. (1981) reported a RD_{50} of 3,373 ppm.

3.3. Neurotoxicity

3.3.1. Non-human Primates

Weiss et al. (1979) evaluated the capacity of squirrel monkeys to selfadminister toluene as a model of abuse. Monkeys (number not specified) previously trained to self-administer drugs on a single response were tested with toluene at concentrations of 0, 560, 1,000, 3,000, or 10,000 ppm during 1-h sessions. Pushing a button delivered a 15-sec exposure to toluene vapor. The highest rate of response (141 responses/h) was at 1,000 ppm. This rate decreased thereafter with increasing concentrations.

Taylor and Evans (1985) subjected adult female cynomolgus macaques to 50-min head-only exposures to toluene at 0, 100, 200, 500, 1,000, 2,000, 3,000,

or 4,500 ppm and simultaneously tested for delayed matching-to-sample behavior as a measure of cognitive function. Monkeys were exposed singly to each concentration, with each monkey tested twice at each concentration. This procedure took 6 weeks. Previously, two of the monkeys had been exposed at 100 ppm and one monkey had been exposed at 1,000 ppm toluene for 6 h/day, 5 days/week for 90 days. Toluene concentration was monitored continuously with an infrared gas analyzer. Responses at 100 and 200 ppm were similar to those during the control sessions. The responses at 500 and 1,000 ppm were lower than, but not significantly different from the control responses. Cognitive func

tion was impaired at 2,000 ppm or higher, as indicated by an increase in response time and a decrease in accuracy of matching. Response time at 4,500 ppm increased by 0.26 sec over the control response time, and monkeys failed to respond during the second half of the session. Most monkeys remained awake at 4,500 ppm, but failed to respond. The effect was characterized as an attention deficit with no specific memory effect. Expired carbon dioxide, measured during the exposures, displayed an inverted U-shaped concentration-effect curve.

3.3.2. Rats

Many of the nonlethal studies in rats evaluated the acute CNS effects of toluene exposure (Table 6-5). Most of these studies demonstrated the biphasic nature of reaction to toluene: an initial stimulatory effect followed by CNS depression. The effects of 0.5-, 1-, 2-, and 4-h exposures at 150 ppm in male Sprague-Dawley rats were evaluated using a multiple fixed ratio-fixed interval (FR-FI) schedule of reinforcement (Geller et al. 1979). Both schedules of reinforcement were increased during the shorter exposures (0.5 and 1 h), showing a stimulatory effect, and decreased during the longer exposures (2 and 4 h) compared with controls. Values for individual rats were presented graphically; aside from the general pattern of an increase followed by a decrease in rate of responding over time, there were considerable individual differences among toluene-exposed rats. Furthermore, the pattern of the control session over time was not provided.

The acute effects of toluene inhalation on the detection of auditory signals (sensitivity index and response index) were evaluated by Bushnell et al. (1994). Male Long-Evans rats were exposed to toluene at 0, 1,000, 1,500, or 2,000 ppm for 1 h. Toluene eliminated the normal increase in sensitivity index that occurred over a session. The responsitivity index was decreased by toluene at the beginning of each session but returned to control levels during exposure at 1,000 or 1,500 ppm, and within 40 min of exposure at 2,000 ppm was increased above control levels. Increases in latency were concentration- and time-dependent.

Groups of four adult male Long-Evans rats weighing 350 g were exposed to toluene at 0, 1,200, 1,600, 2,000, or 2,400 ppm for up to 70 min (Bushnell et al. 2007a), and responses were measured at five 12-min intervals from 22-70 min

(22, 34, 46, 58 and 70 min). Each rat inhaled one concentration/day and each rat was exposed at each concentration over the course of 5 days; concentrations were administered in counter-balanced order. Rats were previously trained in a signal-detection task consisting of a food reward in response to a visual signal. There was a concentration-related change in a signal-detection task, with accuracy (attention to the signal) decreased and response time increased, but the number of false hits was not affected. Mean response times in the control group (exposure to air) and the group exposed to toluene at 2,400 ppm were approximately 0.4 sec and 1.9 sec, respectively. A doubling in the response time (from

TABLE 6-5 Neurbehavioral Effects of Acute Inhalation Exposure to Toluene in Rats

Concentration (ppm)	Duration	Effects	Reference
150	0.5, 1 h	Stimulatory effect, multiple schedule performance.	Geller et al. 1979
	2, 4 h	Reduced performance.	
0, 1,200, 1,600, 2,000, 2,400	22, 34, 46, 58, 70 min	Signal detection task: concentration- and duration-related reduction in attention and increase in response time; no effect on false hits; NOAEL for doubling of reaction time was 1,600 ppm for 34 min and 2,000 ppm for 46 min.	Bushnell et al. 2007a
178, 300, 560	2 h	Increased activity (for reward).	Wood and Cox 1995
1,000, 1,780	2 h	Increased activity, then return to control rate.	
3,000	2 h	Increased activity, then decrease below control rate.	
810	4 h	Threshold, decreased unconditioned reflex.	Mullin and Krivanek 1982
1,660	4 h	Increased number of failures.	
3,100	2 h	Decreased conditioned avoidance response.	
6,500	1 h	Rats failed numerous test; prostrate after 2 h.	
1,340	1-4 h	EC_{50}: most sensitive unconditioned reflex (calculated).	
125, 250, 500	4 h	Decreased conditioned avoidance responses.	Kishi et al. 1988
1,000, 2,000	4, 2 h	Increased incorrect responses and reaction time.	
4,000	4 h	Excitation, increased response rate, ataxia.	
1,000, 1,500, 2,000	1 h	Initial decrease in detection of auditory signals at all concentrations followed by return to control levels.	Bushnell et al. 1994
1,000	4 h	Little effect on avoidance responses.	Shigeta et al. 1978
3,000	4 h	Changes in response pattern.	

(Continued)

TABLE 6-5 Continued

Concentration (ppm)	Duration	Effects	Reference
1,000, 1,780, 3,000	2 h	1,780 and 3,000 ppm: concentration-dependent increase in response rates to food reward despite electric shock punishment.	Wood et al. 1984
3,000	4 h	Ataxia.	
1,000	4 h	No change in behavior (number of rearings).	Takeuchi and Hisanaga 1977
2,000	4 h	Increased rearings and seizures.	
4,000	4 h	Excitation followed by narcosis.	
2,000	4 h	Increased number of lever presses to avoid shock; no change in avoidance behavior.	Harabuchi et al. 1993
4,000	4 h	Increased number of lever presses to avoid shock; decrease in avoidance response.	
1,700	4 h	No decrease in activity following exposure.	Miyagawa et al. 1986
3,400	4 h	Activity decreased by 31% followed by recovery.	
5,100	4 h	Inactivity followed by partial recovery.	
2,000	4 h	Increased locomotor activity.	Wada et al. 1989
4,000	4 h	Decreased conditioned avoidance responses.	
6,000, 8,000	4 h	Decreased conditioned avoidance responses, ataxia, narcosis.	
1,333, 2,667 or 8,000 (five 15-30 min peaks)	7.5 h	Effects on visual discrimination; increased motor activity; return to baseline on following day.	van Asperen et al. 2003
2,500	1 h	No effect on motor activity during exposure.	Hinman 1987

5,000	1 h	Increased locomotor activity.
10,000	1 h	Increased activity followed by slight decrease.
15,000	1 h	Increased activity followed by cessation of activity.

0.4 sec to 0.8 sec) compared with controls was evident at exposures of 2,000 and 2,400 ppm for 34 min and at 1,600 ppm for 46 min. The NOAEL for this effect was noted at 1,600 ppm for 34 min and at 2,000 ppm for 46 min. A doubling in reaction time was identified by Dr. Bushnell as a relatively unambiguous demarcation of a clear effect on CNS function and comparable to the effect level observed in ethanol intoxication (P.J. Bushnell, personal communication, 2013; Appendix D). A physiologically-based toxicokinetic (PBPK) model quantitatively predicted behavioral effects based on concentrations in the brain (Bushnell et al. 2007a), but not predictions based on the area under the curve (AUC) of exposure or on the AUC of brain toluene concentration. Rats developed a tolerance to toluene after repeated exposure at high concentrations during performance testing (Oshiro et al. 2007), and performance was also affected by motivation as reward or punishment (Bushnell et al. 2009).

Wood and Cox (1995) exposed 12 male Long-Evans rats to toluene at 178, 300, 560, 1,000, 1,780, or 3,000 ppm for 2 h and performed behavioral evaluations of nose-poking on a probabilistic schedule of food delivery. Animals served as their own controls, and exposures were repeated. Exposure sessions were 3-4 days apart. The general pattern of responses over the 2-h session for all exposures including the control was an initial high response rate during the first 20 min of the exposure followed by a tapering-off effect; the number of responses also generally increased with increasing concentration. This pattern of concentration-dependent increased numbers of responses over the control value was observed except at the higher doses. During the 3,000-ppm session, the initial high rates of responding fell below the control rates after 50 min of exposure. During the session at 1,780 ppm, the rates returned to control values by the end of the exposure. Between 178 and 560 ppm, responses over the number of control responses increased in both concentration-dependent and time-dependent manners. The authors described these results as biphasic concentration-effect, time-effect, and concentration-response functions at the higher concentrations. A weighted regression analysis determined that a response increase of 10% in all animals would be achieved at a concentration of 182 ppm, with a lower 95% confidence limit of 157 ppm. In an earlier study with a similar protocol (Wood et al. 1984), rats trained to press a lever for a food reward increased their rate of response following 2-h exposures to toluene at 1,780 and 3,000 ppm in spite of electric shock punishment.

Mullin and Krivanek (1982) tested unconditioned reflexes and conditioned reflex tasks in groups of six 5-week-old male Charles River CD rats exposed to toluene at 0, 800, 1,600, 3,200, or 6,400 ppm for 4 h. Measured concentrations were 810, 1,660, 3,100, and 6,250 ppm. Unconditioned reflex tests consisted of locomotor activity, coordination, corneal reflex, and righting reflex. The conditioned reflex involved shock avoidance. A few rats began to fail unconditioned reflex tests at 800 ppm (one of 16 tests); the 1-, 2-, and 4-h EC_{50} for the most sensitive test were all 1,340 ppm. Rats showed excitement during the

first halfhour of exposure at 3,100 ppm, decrements in conditioned avoidance were observed after exposure for 1 h, and rats began to show prostration by 2 h. At 6,250 ppm, rats failed numerous tests at 1 h and were prostrate at 2 h, at which time the test was terminated. There were no mortalities.

A group of eight male Wistar rats were exposed to toluene at 0, 125, 250, 500, 1,000, 2,000, and 4,000 ppm for 4 h on separate days (Kishi et al. 1988). Exposures were in ascending order of concentration. Chamber concentrations were measured with a gas chromatograph. This experiment incorporated shockavoidance behavioral observations during toluene exposure. Rats were exposed to toluene or air for 4 h a day, and the interval between exposures was 10-20 days to avoid lingering effects. Rats were tested continuously for 2 h after each exposure. When rats were exposed at 125, 250, or 500 ppm, a decline in conditioned avoidance responses 20 min into the exposure were found compared with baseline. However, results were variable, and there was no concentrationresponse relationship. Rats almost completely recovered during the postexposure period. After exposure at 1,000 ppm for 4 h or 2,000 ppm for 2 h, there were concentration-related increases in lever presses and incorrect responses (implying excitation), acceleration of the reaction time, and decreases in the effective avoidance response rate. At the beginning of the 4,000 ppm exposure, the response rate increased and then gradually decreased until slight ataxia was observed in six of eight rats.

A similar study by Wada et al. (1989) also used shock-avoidance training as a measure of CNS impairment when male Wistar rats (in groups of eight) were exposed to measured concentrations of toluene at 2,000, 4,000, 6,000, or 8,000 ppm for 4 h. Shock avoidance, motor activity, and latency of response were measured immediately after the exposure and at 3 and 6 h and 1, 2, and 3 days postexposure. As in the previous experiment, shock-avoidance responses were decreased in pretrained rats at 4,000 ppm and higher, but recovery was achieved within 3-6 h postexposure. Also, at 2,000 and at 4,000 ppm, locomotor activity was transiently increased. Paradoxically, at 4,000 ppm, response latencies were increased. The authors also reported a failure in rats exposed at 6,000 or 8,000 ppm to avoid electrical shock, and the percentage of escape responses was decreased as well. Locomotor activity was dramatically decreased at those concentrations; therefore, ataxia and narcosis could have contributed to impaired avoidance performance.

Takeuchi and Hisanaga (1977) exposed groups of male Wistar rats to toluene at 1,000, 2,000, or 4,000 ppm for 4 h. They observed general activity and measured EEG activity. No change in general activity was found at 1,000 ppm, as evidenced by the number of rearings, and there were few changes in the EEG results. At 2,000 ppm, there were increased rearings and occasional myoclonic seizures; these changes were accompanied by increases of high-frequency EEG activity and a disturbance of the sleep pattern. At 4000 ppm there was increased activity followed by narcosis. These rats also experienced myoclonic seizures. All sleep pattern activity was disturbed. Shigeta et al. (1978) also found that a 4h exposure at 1,000 ppm had little effect on avoidance responses (to an electrical

shock) of adult male Wistar rats. At 3,000 ppm, the responses increased, but the inter-response pattern shortened, with the result that there was no significant

difference in shock counts. Behavior recovered in an hour. Harabuchi et al. (1993) also found little difference in shock avoidance in male Wistar rats exposed to toluene at 2,000 ppm for 4 h. At 4,000 ppm, lever presses in response to a warning sound were increased, but shock avoidance responses were significantly decreased soon after exposure began.

A biphasic recovery curve for a variable interval response schedule (lever press for food reward) was observed by Miyagawa et al. (1986). Young male Sprague-Dawley rats were exposed in groups of four to toluene at 1,700, 3,400, or 5,100 ppm for 4 h. The response rate was then assessed at recovery intervals of 0-30, 30-60, 60-90, and 90-120 min. The same rats were used at each concentration for the four response times (four different days). At 1,700 ppm, the behavioral response rate was increased by about 40% compared with baseline levels, and duration of recovery period did not influence activity. A decrease in responses compared with baseline was observed in the 3,400-ppm group immediately after exposure, but the response rate increased to greater than baseline during the next 30-120 min. Immediately after exposure at 5,100 ppm, an almost total decrease in responses was observed, followed by a linear increase with respect to duration of recovery period. The authors also noted that at low brain toluene concentrations an increase in response rate occurs, which is reversed at higher concentrations so that an inverted U-shaped curve is obtained for the relationship between lever-pressing behavior and toluene concentration in the brain.

A biphasic concentration-effect relationship was observed in male LongEvans rats exposed to increasing concentrations of toluene by Hinman (1987). Six rats were used with some rats being exposed at several concentrations. Spontaneous locomotor activity was monitored continuously during inhalation of toluene at 0, 2,500, 5,000, 10,000, or 15,000 ppm for 60 min. Sham exposures resulted in a period of activity for approximately 30 min followed by period of low activity (habituation). Before each toluene exposure, the rats were allowed a 30-min habituation period during which they adjusted to their surroundings. The pattern of activity during the exposure at 2,500 ppm was the same as that of the control exposure (no increased activity during the exposure). At 5,000 ppm, locomotor activity increased monophasically during exposure and subsequently decreased in the same manner during recovery. At higher concentrations (10,000 and 15,000 ppm), locomotor activity initially increased, but decreased with continued exposure and eventually ceased. The highest concentrations of toluene produced a biphasic recovery, with time to maximum activity and time to recovery dependent on the concentration of toluene during exposure. No rats died during the exposures.

Lammers et al. (2005b) and van Asperen et al. (2002) exposed groups of eight male WAG/RijCrlBR rats to toluene at constant concentrations of 1,333 or

2,667 ppm for 7.5 h or to five peaks of 8,000 ppm for 15 or 30 min, alternating with toluene-free intervals, so that total exposures were to averages of 1,333 or 2,667 ppm, respectively. Visual discrimination was tested prior to, immediately after, and 24 h postexposure. Spontaneous motor activity was monitored continuously from preexposure to postexposure. All exposure scenarios resulted in changes in visual discrimination performance, defined as a slowing of response speed and disinhibition of responding (results presented graphically). Short-term fluctuating exposure scenarios resulted in greater effects on behavior than exposures at a constant concentration. But effects were time- and exposure-scenariorelated. Visual discrimination and activity returned to preexposure levels by 24 h postexposure.

3.3.3. Mice

Several studies in mice have focused on the neurobehavioral effects of acute toluene exposure (Table 6-6). Bushnell et al. (1985) exposed groups of eight male C57BL/6 mice to toluene at 0, 100, 1,000, 3,000, or 10,000 ppm for 72 min on successive days to measure effects on motor activity and carbondioxide production. The same group was used for all exposures (the first exposure was at 10,000 ppm). For the 10,000-ppm exposure, mice were placed into the chamber before the vapor was generated for safety reasons. The concentration climbed exponentially from 0 to 10,500 ppm over the course of the exposure ($t_{1/2}$ = 15 min). Activity was measured by interruptions of a photobeam in a computerized system. Activity was similar during exposure to air and to toluene at 100 ppm (activity followed by a gradual decline). At 1,000 ppm, motor activity began to increase above that of the control after 60 min. At 3,000 ppm, the increased activity began 12 min after the start of the experiment and continued throughout the exposure. At 10,000 ppm, activity was similar to that of the control group during the first 24 min, after which it declined precipitously, reaching 0 by 48 min. In the latter experiment, toluene was allowed to decline in the chamber over a period of 72 min. Carbon-dioxide production was initially suppressed at 1,000 ppm and higher. At vapor concentration below 6,000 ppm, animals recovered and became hyperactive 24 min post-exposure. In a second experiment, exposure of a separate group of mice to toluene at 3,000 ppm for 5 h/day for 5 days had no effect on activity when measured 30-90 min after exposure. In a third experiment, groups of eight mice were exposed to toluene at 0, 100, 1,000, or 3,000 ppm for 5 h/day, 5 days/week for 12 weeks. These exposures affected minute volume of expired carbon dioxide, but did not decrease postexposure locomotor activity or have an effect on body weight.

Using the inverted screen test to measure motor performance, Moser and Balster (1985) exposed groups of 12 CD-1 mice to several undefined concentrations of toluene for periods of 10, 30, or 60 min. Within 60 sec after exposure, mice were tested for the ability to hold onto or climb to the top of a screen rotated 180°. Significantly lower EC_{50} values were obtained at each increase in exposure duration; for the 10-, 30-, and 60-min durations, the EC_{50}

values were 2,959, 2,012, and 1,445 ppm, respectively. The authors also presented recovery

TABLE 6-6 Neurobehavioral Effects of Acute Inhalation Exposure to Toluene in Mice

Concentration (ppm)	Duration	Effects	Reference
100	72 min	No effect on locomotor activity.	Bushnell et al. 1985
1,000	72 min	Increased activity after 60 min.	
3,000	72 min	Increased, sustained activity after 12 min.	
10,000	72 min	No effect on activity for 24 min followed by narcosis.	
200, 400, 800	30 min	No change in operant behavior.	Moser and Balster 1981
1,600	30 min	Increased responding, decreased reinforcement.	
3,200	30 min	Ataxia.	
6,400	30 min	Narcosis.	
2,959	10 min	EC_{50} for inverted screen test.	Moser and Balster 1985
2,012	30 min	EC_{50} for inverted screen test.	
1,445	60 min	EC_{50} for inverted screen test.	
≥2,000	20 min	Functional observational battery changes: abnormal posture, abnormal gait, decreased arousal, decreased rearing.	Tegeris and Balster 1994
100, 250, 500, 1,000, 2,000	30 min	Concentration-related increase in locomotor activity.	
4,000, 6,000, 8,000	30 min	Biphasic locomotor activity; overall concentration-related decrease in locomotor activity; narcosis at end of 30-min session at 8,000 ppm; slight concentration-related decrease in schedule-controlled behavior at 100-8,000 ppm.	Bowen and Balster 1998
500	4 h	No effect on schedule-controlled behavior.	Glowa 1981
1,000	4 h	Increased rate of responding.	
2,000	4 h	Decreased rate of responding.	
1,657	30 min	EC_{50} for decreased responding for schedule-controlled behavior.	Glowa et al. 1986
722-1193	4 h	31-74% decrease in immobility in “behavioral despair” swimming test.	De Ceaurriz et al. 1983
2,600	1-1.5 h	Ataxia, no loss of consciousness at 3 h.	Bruckner and Peterson 1981a, b
5,200	45 min	Immobility, loss of consciousness at 1.5 h.	
12,000	10 min	Loss of consciousness.	

times with respect to maximum concentrations tested for each duration. There was only a 5-min recovery time for a 10-min exposure at 5,000 ppm. However, for the 30- and 60-min exposures at 3,000 and 2,000 ppm, respectively, there was a 30-min recovery period.

In a study of operant behavior, Moser and Balster (1981) exposed groups of eight CD-1 mice individually to toluene at 200, 400, 800, 1,600, 3,200, or 6,400 ppm for 30 min in a static-exposure chamber. Tests were performed during a 15-min postexposure period. Diet was maintained at 80% free feeding weight, and sweetened milk was used as a reinforcer for lever-press responding. Reinforcement occurred only with a 10-sec pause between responses. Response rates increased in the groups exposed at up to 3,200 ppm; at 6,400 ppm, the response rate decreased below that of the control group. At concentrations above 800 ppm, the rate of reinforcement decreased in a concentration-dependent manner. When removed from the exposure cage, mice exposed at 1,600 ppm were excitable and mice exposed at 3,200 ppm had marked ataxia. Animals exposed at 6,400 ppm were almost anesthetized. As part of the same report, mice were exposed to toluene at 6,000 ppm for 30 min/day, 5 days/week for 7 weeks; operant testing was carried out with the acute exposures. All mice survived the repeated exposures and appeared in good health. Response rate was variable, and the reinforcement rate remained low. Operant behavior returned to baseline 3 days after exposure ended.

Tegeris and Balster (1994) exposed groups of eight male Swiss mice to toluene at 0, 2,000, 4,000, or 8,000 ppm for 20 min. During the last 2 min of the exposure, the mice were observed for neurologic deficits. A functional observational battery (FOB) was administered following exposures. Effects occurred both during and after exposures and were concentration-related. Motor incoordination (abnormal gait), decreased muscle tone, and equilibrium changes, as well as decreased rearing occurred at 2,000 ppm and higher. Loss of the righting reflex occurred at 4,000 ppm. By the end of the exposure at 8,000 ppm, all mice were essentially anesthetized. However, recovery was rapid when the rats were removed from exposure. Lacrimation was observed only after exposure at 8,000 ppm. The profile of neurobehavioral effects was similar to that induced by phenobarbital (intraperitoneal injections of 0-40 mg/kg).

In another study, Bowen and Balster (1998) tested locomotor activity and schedule-controlled behavior in adult male CFW mice exposed to toluene at 100, 250, 500, 100, and 2,000 ppm. During 30-min exposures, locomotor activity increased with increasing concentrations; the increases were significant different from controls at concentrations of 500 ppm and higher. Total locomotor activity decreased with increasing concentrations of 4,000, 6,000, and 8,000 ppm. Activity became biphasic, increasing and then decreasing at both 6,000 and 8,000 ppm. By the end of the 8,000-ppm exposure session, the mice were essentially immobile and appeared anesthetized. The effect of these concentrations on schedule-controlled behavior (pressing a lever for a liquid reward) was also studied. According to the authors, the expected increases in rates of behav

ior were not observed. Instead, there was a concentration-related decrease in responding, which was most obvious at 4,000 ppm and higher.

The behavioral effects of toluene exposure in CD-1 mice were also evaluated by Glowa et al. (1986). A fixed-interval (FI) 60-sec schedule of milk delivery after a response (breaking a beam of light), with an alternating series of eight consecutive rewards followed by an inter-series time out of 30 min, was developed as a means of behavioral assessment. Nominal concentrations of toluene at 250 to 4,000 ppm were added to the sealed exposure chambers. Concentrationeffect curves were constructed by exposing mice to incremental additions of toluene at 30-min intervals. The rate of responding in mice exposed to toluene at 700 ppm was increased, and higher concentrations progressively reduced responding. The calculated EC_{50} for a reduced rate of responses was 1,657 ppm.

In a similar study by Glowa (1981), the effects of 4-h exposures to toluene for 5 consecutive days produced similar results. The FI 60-sec milk presentation was again used, with 10-min sessions of milk availability followed by 25-min periods were responding had no consequences. The effects of toluene on schedule-controlled behavior were concentration-dependent: 500 ppm had little effect on the rate of responding, 1,000 ppm consistently increased rates of responding, and 2,000 ppm consistently decreased rates of responding.

Four different toluene exposure concentrations of 722, 785, 977, or 1,193 ppm were evaluated in a "behavioral despair" swimming test with male Swiss OF1 mice (De Ceaurriz et al. 1983). Rodents forced to swim in a restricted space became immobile after approximately 3 min. After 4-h exposures, all four toluene concentrations significantly decreased the mean duration of immobility (increased activity during a 3-min test period). A concentration-effect relationship was observed at the lowest concentration of toluene producing a 31% decrease in immobility and successively increasing concentrations producing 36, 54, and 74% decreases for exposures at 722, 785, 977, or 1,193 ppm, respectively. The concentration associated with a 50% decrease in immobility was 915 ppm.

Bruckner and Peterson (1981a) exposed groups of four male ICR mice to toluene at concentrations of 2,600, 5,200, or 12,000 ppm for up to 3 h to evaluate the narcotic potency, speed of onset, and duration of CNS-depressant effects of inhaled toluene. Five reflex tests (balance, visual placing, grip strength, tail pinch, and righting reflex) were used to evaluate the onset of loss of reflexes/narcosis during the exposures. Tests were performed at 5- to 15-min intervals. Seven-week-old mice exposed to toluene at 12,000 ppm became depressed very rapidly and were unconscious within 15 min. Mice exposed to toluene at 5,200 ppm became immobile within 45 min and unconscious after approximately 1.5 h. At 2,600 ppm, mice became ataxic in 1-1.5 h and, within 2 h, were immobile in the absence of stimulation, although consciousness was not lost within the 3-h test period. Four-week-old mice tested separately were slightly more sensitive to toluene-induced narcosis than were 8- and 12-week old mice. Rats, tested at the same concentrations, were slightly less sensitive than mice. Specific data were not provided for rats.

Bruckner and Peterson (1981a) also reported on recovery times of mice following 5-, 10-, or 20-min exposures to toluene at concentrations of 4,000, 8,000, or 12,000 ppm. Seven-week old mice were tested in groups of five. Minimal decrements in reflexes were observed at 4,000 ppm for up to 20 min. Recovery to preexposure performance and reflexes took 10 min or less. Depression was greater and recovery took longer with increasing concentrations and increasing exposure durations. For example, animals became immobile and lost consciousness during the 10- and 20-min exposures at 12,000 ppm, but full recovery took place after breathing fresh air for 12 and 37 min, respectively.

In exposures designed to approximate human solvent abuse episodes, mice and rats were subjected to seven consecutive inhalation cycles consisting of 10min exposures to toluene at 12,000 ppm followed by a 20-min solvent-free recovery period (Bruckner and Peterson 1981b). Signs of ataxia characteristic of inebriation in humans were observed after 2-3 min and unconsciousness was observed in about 10 min. Although mice were depressed to a greater degree than rats, the mice exhibited marked recovery during each fresh air interval. Recoveries in rats progressively declined over the 190-min regimen. No deaths were reported.

3.3.4. Rabbits

Kobayashi (1985) described effects of toluene in rats exposed at 4,000 ppm either in air or mixed with oxygen. For both mixtures, the observed responses included Cheyne-Stokes respiration (within 2-3 min), arrhythmia, increased blood pressure, and slow wave hypersynchronies in cortical and subcortical EEGs which progressed to pH decreases and arousal reaction disappearance in the sensorimotor cortex and hippocampus. Most of these effects occurred within 15-20 min. Finally, grand mal seizures were followed by postictal depression. The respiratory acidosis shifted gradually to metabolic acidosis with continued exposure.

3.4. Developmental and Reproductive Toxicity

In a review of reproductive and developmental toxicity in animal models, reduction of late fetal body weight and retardation of skeletal development were the most consistent fetotoxic effects (Donald et al. 1991). Although intrauterine growth was retarded, there is little evidence that exposure to toluene causes teratogenic effects. Selected studies identified in the literature are summarized in Table 6-7.

Although continuous exposures and 12-h exposures to toluene at low concentrations appeared to be maternally toxic in rat and mice (Hudak and Ungvary 1978; Tatrai et al. 1980; Ungvary and Tatrai 1985), the lowest concentration that retarded fetal growth in the rat was 1,200 ppm when administered under developmental and reproductive guidelines suggested by EPA (6 h/day during organogenesis) (Thiel and Chahoud 1997).

TABLE 6-7 Reproductive and Developmental Toxicity of Toluene in Animals

Concentration (ppm)	Duration	Effects	Reference
Rat			
266	GD 1-21 (8 h/d)	Slightly reduced fetal body weights.	Hudak and Ungvary 1978
399	GD 1-8 (24 h/d)	Reduced fetal body weight; maternal deaths.	
399	GD 9-14 (24 h/d)	No effect on fetuses; maternal deaths.	
100, 400	GD 6-15 (6 h/d)	No effect at either concentration.	LBI 1978
266	GD 7-14 (24 h/d)	Delayed skeletal development.	Tatrai et al. 1980
100, 500, 2,000	80 d before mating and through lactation	Reduced fetal body weight (by 8%) at 2,000 ppm; no evidence of maternal toxicity.	API 1985
750, 1,500, 3,000	GD 6-15 (6 h/d)	No fetal effects at 750 ppm; minimal reduction in mean litter and fetal weights and unossified sternebrae at 1,500 and 3,000 ppm; maternal clinical signs at all concentrations.	API 1993
300, 600, 1,000, 1,200	GD 9-21 (6 h/d)	Reduced fetal and dam body weights at 1,200 ppm; higher mortality up to weaning at 1,200 ppm; no neurobehavioral or reproductive deficits in F_1 generation.	Thiel and Chahoud 1997
1,200, 1,800	GD 7-19	No effects on reproductive parameters.	Dalgaard et al. 2001
1,800	GD 7-20 (6 h/d)	Increased neuronal apoptosis in brain of male offspring at PND 21.	
1,500	GD 7-20 (6 h/d)	Reduced fetal birth weight and lower maternal weight gain.	Hougaard et al. 2003
600, 2,000	GD 7-17 (6 h/d)	No effect at 600 ppm. At 2,000 ppm: fetal and dam body weight decreases; no anomalies or neurobehavioral effects on offspring but fetal mortality and growth retardation.	Ono et al. 1995
600, 2,000	6 h/d; females: 14 d pre-gestation to GD 7; males: 90 d (60 d prior to mating)	Fertility and mating performance unaffected at both concentrations. Males: no clinical signs at 2,000 ppm. Females: salivation, lacrimation, and decreases in body weight and food consumption; increased fetal mortality at 2,000 ppm.	Ono et al. 1996

(Continued)

TABLE 6-7 Continued

Concentration (ppm)	Duration	Effects	Reference
Mouse			
133, 399	GD 6-13 (24 h/d)	Significantly reduced fetal weight at 133 ppm; all dams died at 399 ppm.	Hudak and Ungvary 1978
133, 266, 399	GD 6-15 (12 h/d)	Significantly reduced fetal weight at 266 ppm; all dams died at 399 ppm.	Ungvary and Tatrai 1985
200, 400	GD 7-16 (7 h/d)	Increased incidence of dilated renal pelves at 200 ppm but not at 400 ppm; increase in fetuses with 13 ribs (normal number for mice).	Courtney et al. 1986
100, 1,000	GD 1-17 (6 h/d)	Significant increase in incidence of fetuses with extra (14) ribs at 1,000 ppm.	Shigeta et al. 1981
Rabbit			
30, 100, 300, 500	GD 6-18 (6 h/d)	No effects on dams or fetuses at any concentration.	Klimisch et al. 1992

Abbreviations: GD, gestation day; PND, postnatal day.

Male F344/N rats and B6C3F$_1$ mice evaluated in the toluene inhalation studies of NTP (1990) exhibited no compound-related effects on sperm count or motility when exposed at concentrations of 3,000 ppm or less for 14 weeks or at 1,200 ppm or less for 2 years. No histopathologic lesions were observed in the epididymis, prostate, or testes either species.

Male SD rats exposed to toluene at 600 ppm for 6 h/day for 90 days exhibited a decrease in sperm count of 13%; when exposed at 2,000 ppm under the same protocol, the sperm count decreased significantly by 26% and the weight of the epididymis declined by 15% (Ono et al. 1996); these changes had no effect on mating performance or fertility as characterized by fertility and copulation indices.

3.5. Genotoxicity

Toluene has been extensively studied for genetic toxicity both in vitro and in vivo. There is an overwhelming body of evidence that indicates that toluene is not genotoxicy. Very few positive studies exist, and the few that are positive have confounding factors which limit their reliability and relevance (NTP 1990). These confounding factors include the purity of the toluene in the case of in vitro studies and the presence of other chemicals and smoking habits in studies of workers. The metabolites of toluene, such as benzyl alcohol, are also nongenotoxic (NTP 1990). While the majority of toluene metabolites are nongenotoxic, the minor metabolite, o-cresol, has shown genotoxicity in some in vitro tests with Chinese hamster ovary cells (ATSDR 2008). Selected studies reviewed in CIR (1987), NTP (1990), IARC (1999), and ATSDR (2000) are discussed below.

Toluene was assayed for mutagenicity using the Ames Salmonella/microsome assay by Bos et al. (1981). In this study, toluene was unable to revert *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 either with or without metabolic activation by S9 mix derived from livers of rats either untreated or induced with Aroclor 1254. Several other studies in *S. typhimurium* were also negative for gene mutation and growth inhibition due to DNA damage (Mortelmans and Riccio 1980; Anderson and Styles 1978; LBI 1978; Florin et al. 1980; Nestmann et al. 1980; Snow et al. 1981; Spanggord et al. 1982; Haworth et al. 1983). Studies in *Bacillus subtilis* (McCarroll et al. 1981a), *Escherichia coli* (Fluck et al. 1976; McCarroll et al. 1981b; Mortelmans and Riccio 1980), and *Saccharomyces cerevisiae* (LBI 1978; Mortelmans and Riccio 1980) were also negative for genotoxic effects.

In vitro studies using mouse lymphoma L5178Y cells (LBI 1978; McGregor et al. 1988) or Chinese hamster ovary cells (Evans and Mitchell 1980) were also negative.

Mammalian in vivo studies in rats have produced some positive, yet questionable, results. In one inhalation study, rats that were exposed to toluene at 80 ppm for 4 h/day for 4 months (Dobrokhotov and Enikeev 1975) had an increased incidence of chromosomal aberrations. Three oral studies in rats

(Dobrokhotov 1972; Lyapkalo 1973; and Sina et al. 1983) also observed chromoso*336 Acute Exposure Guideline Levels*

mal aberrations or DNA single-strand breaks. However, three of these studies used toluene preparations of unspecified purity and could have been contaminated with benzene (a known clastogen). The results observed in the study by Sina et al. (1983) were probably due to cell lysis, because the single-strand breaks were only observed when cytotoxicity was greater than 30% (NTP 1990).

In vivo studies in the mouse have produced negative results. Several studies in the mouse were negative for genotoxic effects when several different parameters were evaluated. These included micronucleus induction (Kirkhart 1980; Gad-El-Karim et al. 1984), sperm-head abnormalities (Topham 1980), dominant-lethal mutations (LBI 1981), sister-chromatid exchange (Tice et al. 1982), and chromosomal aberrations (Gad-El-Karim et al. 1984).

3.6. Subchronic and Chronic Toxicity and Carcinogenicity

Jenkins et al. (1970) exposed Sprague-Dawley rats to repeated or continuous concentrations of toluene to study long-term effects on mortality, body weight, and hematology parameters. A group of 15 male and female rats was exposed to toluene at 1,085 ppm for 8 h/day, 5 days/week for 6 weeks, and a group of 13 male and female rats exposed continuously at 107 ppm for 90 days. A control group was composed of 14 rats. No rats died in the repeated-exposure study. Two rats continuously exposed to toluene died, one on day 28 and the second on day 56. Rats in both treatment groups gained more weight than the control group; however, rats in the treatment groups were heavier than the controls at the start of the study. There were no apparent effects on hemoglobin, hematocrit, or leucocyte count. No further details were reported.

Poon et al. (1994) exposed groups of 10 male and 10 female SpragueDawley rats to toluene at 30 or 300 ppm for 6 h/day, 5 days/week for 4 weeks. The higher concentration caused mild biochemical changes (increased serum alkaline phosphatase activity in males), an occasional moderate reduction in follicle size of thyroid gland cells, and subepithelial nonsuppurative inflammation of the nasal passages.

There is no evidence to indicate toluene produces increased incidences of tumors in rats or mice. Gibson and Hardisty (1983) conducted a chronic toxicity and carcinogenicity inhalation study in male and female F344 rats. Groups of 120 animals were exposed to toluene at 0, 30, 100, or 300 ppm for 6 h/day for 5 days/week for up to 2 years. Subgroups of animals were killed after 6, 12, and 18 months for interim evaluations. There were no treatment-related effects on hematology or clinical-chemistry parameters and no tissue or organ lesions attributable to treatment. No increases in the incidences of neoplasms in treated rats compared with controls were found. Because IARC (1989) judged that the test concentrations may have been low, NTP (1990) conducted a second series of oncogenic bioassays in rats and mice. In those studies, groups of 60 male and 60

female F344/N rats and 60 male and 60 female B6C3F$_1$ mice were exposed to toluene at 120, 600, or 1,200 ppm for up to 2 years (6.5 h/day, 5 days/week). The results revealed no evidence of carcinogenicity in treated animals compared with concurrent controls. Mild degeneration of the nasal cavity olfactory and respiratory epithelium was observed at 600 and 1,200 ppm. Because these effects on the respiratory system were not observed at a higher concentration (3,000 ppm) in a 15-week study, also conducted by NTP (1990), they can be attributed to the repeated nature of the chronic exposure regime. The NOAELs for carcinogenicity and survival were both 1,200 ppm in rats and mice. In addition, no clinical signs were observed in rats or mice. In 1999, IARC concluded that there is evidence suggesting a lack of carcinogenicity in experimental animals treated with toluene.

3.7. Summary

Lethality data on toluene were available for only the rat and mouse. Based on LC_{50} values, the mouse is slightly more sensitive to toluene than the rat. Mouse LC_{50} values ranged from 38,465 ppm for 10 min to 5,320 ppm for 7 h. The highest nonlethal concentrations were 12,000 ppm for 20 min (Bruckner and Peterson 1981a), 5,000 and 6,250 ppm for 2 h (Kojima and Kobayashi 1973; Mullin and Krivanek 1982), and 6,000 ppm for 4 h (Wada et al. 1989).

Toluene, like all CNS depressants and anesthetics, produces an initial excitatory stage followed by narcosis. Except for increased activity, concentrations below 1,000 ppm have little or no effect on gross manifestations of animal behavior (NRC 1981; WHO 1987). At approximately 2,000 ppm, increased motor activity and an increased rate of responding in neurobehavioral tests occur. Higher concentrations suppress activity. In neurotoxicity tests, increased motor activity and response rates (excitation) at low concentrations and decreased activity and responses at higher concentrations are the result of CNS depression (Moser and Balster 1981, 1985; Wood et al. 1983). Increases in activity with no or minor decrements in accuracy on tasks occurred in rats and mice exposed to toluene at 1,000-2,000 ppm (Mullin and Krivanek 1982; Kishi et al. 1988; Wood and Cox 1995). Mice exposed at approximately 2,000 ppm for short periods of time began to fail equilibrium tests in some studies (Moser and Balster 1985; Tegeris and Balster 1994), but had increased activity in others (Kishi et al. 1988; Wada et al. 1989). Mice exposed at 5,200 ppm became immobile after 45 min and lost consciousness after 1.5 h (Bruckner and Peterson 1981a). The neurologic deficits are similar to those observed in humans. Unfortunately, the onset of neurobehavioral deficits is not readily observable in rodents, so extrapolation to humans is difficult. Furthermore, the increased activity of rodents at low concentrations is not clearly observable in humans.

A number of developmental studies have reported fetotoxicity, including reduced fetal weight and retarded skeletal development, but no evidence of teratogenicity. Continuous exposures and 12-h exposures to relatively low concentrations of toluene appeared to be more toxic to pregnant rat and mice

(Hudak and Ungvary 1978; Tatrai et al. 1980; Ungvary and Tatrai 1985) than 6- to 8-h *338 Acute Exposure Guideline Levels*

exposures at higher concentrations. The lowest concentration that retarded fetal growth of the rat was 1,200 ppm when administered under developmental and reproductive guidelines suggested by EPA (6 h/day during organogenesis) (Thiel and Chahoud 1997). These rodent studies duplicate the developmental delays associated with gross toluene exposures in humans.

Studies of acute exposures to toluene at high concentrations and of repeated and chronic exposures show that toluene is relatively nontoxic. Toluene at concentrations that produced unconsciousness failed to produce residual organ damage (Svirbely et al. 1943; Bruckner and Peterson 1981b; NTP 1990). Repeated and chronic exposures at moderately high concentrations (e.g., 1,200 ppm) also failed to produce organ damage (Gibson and Hardisty 1983; NTP 1990). Effects appeared to be limited to reversible liver enzyme-activity changes (Bruckner and Peterson 1981b). In concordance with the available human epidemiologic data, evidence of carcinogenicity from inhalation exposure to toluene has not been substantiated in well-conducted rodent studies. IARC (1999) concluded that there is evidence suggesting lack of carcinogenicity of toluene in experimental animals.

4. SPECIAL CONSIDERATIONS

4.1. Uptake, Metabolism, and Disposition

As shown in controlled-exposure studies with humans and animals, toluene is readily absorbed through the respiratory tract. Uptake is proportional to the concentration in the inspired air, length of exposure, and pulmonary ventilation (Astrand et al. 1972; Astrand 1975; Veulemans and Masschelein 1978; Bruckner and Peterson 1981a). Blood:air partition coefficients of 15-21, measured both in vitro at 37°C and in vivo in humans and laboratory animals, indicate that toluene is readily absorbed into the blood (Astrand et al. 1972; Sherwood 1976; Sato and Nakajima 1979a; Gargas et al. 1989; Pierce et al. 1996a). The pulmonary retention percentage of toluene (measured by concentrations in inspired and expired air) was 50% in healthy male subjects exposed at 50 ppm with a workload of 50 W or at 80 ppm under sedentary conditions (Lof et al. 1990, 1993). Because uptake depends on respiratory rate and cardiac output, both of which increase during exercise, uptake increases during exercise compared with that at rest (Astrand et al. 1972; Carlsson and Lindqvist 1977; Veulemans and Masschelein 1978; Carlsson 1982; Nadeau et al. 2006). In humans, dermal absorption, measured during atmospheric exposures, is about 1% of that measured after respiratory absorption (Kezic et al. 2000).

Toluene can be detected in human blood within 10-15 sec of initiation of an exposure, and reaches 60% of maximum arterial concentrations within 10-15 min at concentrations as low as 100-200 ppm (Astrand et al. 1972; Benignus 1981).

During a 4-h exposure to toluene at 80 ppm under sedentary conditions, approximately 90% of the 4-h blood value was attained at 2 h; steady-state was reached more rapidly under exercise conditions (Hjelm et al. 1988; Lof et al. 1990, 1993). In a study of mice exposed to toluene at 4,000 ppm, arterial blood concentrations did not reach maximum values until about 2 h after the onset of exposure (Bruckner and Peterson 1981a). After the first 20-30 min of inhalation, the ratio of toluene concentration in the brain and blood is constant (Benignus et al. 1981).

Distribution of toluene to body tissues depends on blood flow to the tissue or organ, lipid content of the tissue, rate of metabolism, and duration of exposure. After absorption, toluene is rapidly distributed to highly vascularized tissues, such as the liver, kidneys, and brain. It rapidly accumulates and affects the brain due to that organ's high lipid content (Bruckner and Warren 2001). It is eventually absorbed and stored in adipose tissue; consequently, obese people tend to accumulate more toluene than do lean people (Carlsson and Lindqvist 1977). Male Sprague-Dawley rats exposed to toluene at 550 ppm for 1 h had the following concentrations of toluene in their tissues immediately after exposure: adipose tissue, 87 µg/g; adrenal glands, 56 µg/g; kidneys, 55 µg/g; liver 21 µg/g; and brain, 15 µg/g (Carlsson and Lindqvist 1977).

Absorbed toluene undergoes rapid, extensive metabolism, primarily in the liver (Low et al. 1988; ATSDR 2000). The major pathway of toluene detoxification and elimination is methyl hydroxylation to form benzoic acid followed by dehydrogenation to benzoic acid and conjugation with glycine to form hippuric acid which is excreted in the urine (Figure 6-1). In humans, oxidation of the methyl group by the hepatic cytochrome isozyme CYP2E1 yields benzyl alcohol (Liira et al. 1991; Nakajima et al. 1997). Benzyl alcohol is rapidly oxidized by alcohol dehydrogenase to benzaldehyde, which in turn is converted to benzoic acid by aldehyde dehydrogenases. About 75-80% of the absorbed dose of toluene is metabolized to benzoic acid, which is also a common food constituent. Following conjugation with glycine, benzoic acid is excreted in the urine as hippuric acid (75-80% of the absorbed dose in humans); smaller amounts of benzoic acid are excreted as the sulfate or glucuronide conjugate. Toluene can also be hydroxylated to form *o*-, *m*-, or *p*-cresol, which are conjugated with sulfate or glucuronide and excreted in the urine. The cresols are minor urinary metabolites (less than 1% of the absorbed dose). The remainder of the absorbed dose, about 18%, is eliminated via the lungs as unchanged toluene. Studies with rat liver microsomes indicate that pathways are the same in humans and rats.

Pierce et al. (1999, 2002) measured exhaled toluene and excreted metabolites in 25 men, ages 20-62, who were exposed to ^{2}H-toluene at 50 ppm and unlabeled toluene at 50 ppm through a gated mouthpiece for 2 h while at rest. Metabolites were evaluated for 4 days, and the disposition was as follows: exhaled toluene, 13 ± 6.2%; hippuric acid, 75 ± 6.4%; *o*-cresol, 0.31 ± 0.22%; *m*-cresol, 0.53 ± 0.44%; and *p*-cresol, 11 ± 3.8%. The exhalation rate of toluene was exponentially triphasic, whereas metabolite excretion rates were biphasic. ^{2}Htoluene was cleared slightly faster than unlabeled toluene, but the difference

was small compared with individual differences in toluene kinetics. Body weight, adipose tissue fraction, and blood:air partition coefficient were correlated with

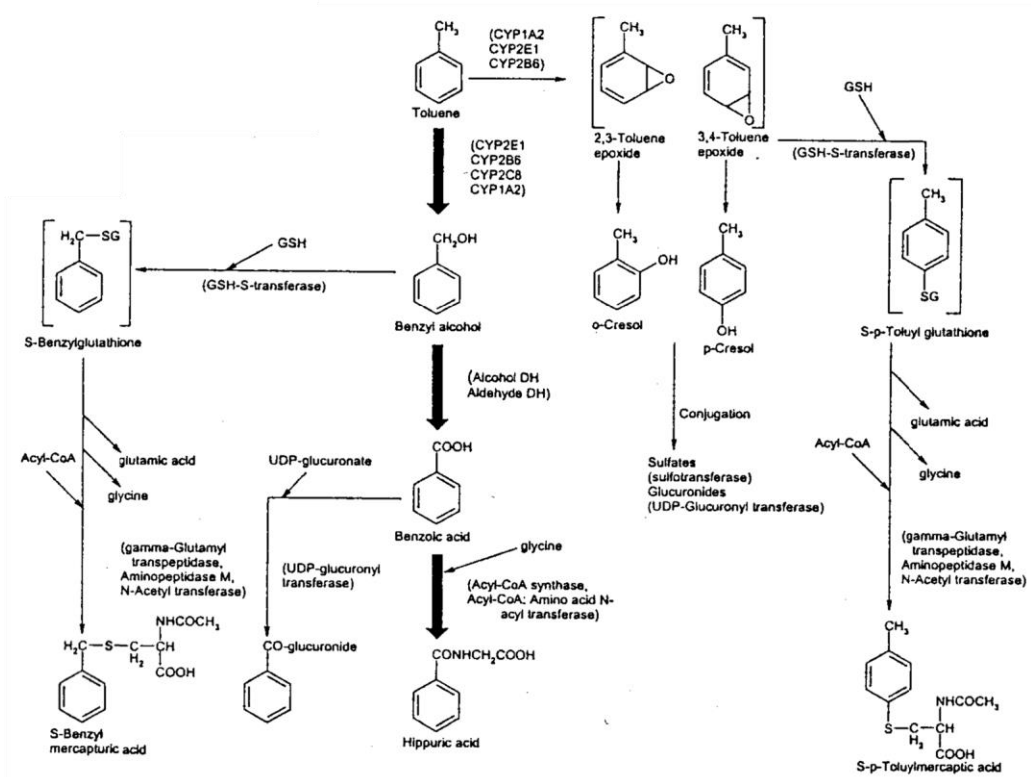

FIGURE 6-1 Metabolism of toluene in mammalian systems (heavy arrows indicate major pathways of metabolism). Source: ATSDR 2000.

terminal half-life, steady-state volume of distribution, and terminal volume of distribution (Pierce et al. 1996a). During the 2-h exposure, a 10-fold interindividual range in venous blood concentrations of toluene was found between the highest and lowest values (ventilation rate differed between these two subjects by a factor of two).

Benoit et al. (1985) reported that following a 90-min exposure of seven human subjects to toluene at 50 ppm, retention at steady-state (measured by elimination in exhaled air) was 83%. In the postexposure period, toluene was eliminated occurred by first order kinetics, with a half-life of 25 min. Lof et al. (1993) found that toluene elimination from the blood of nine human volunteers after exposure at 53 ppm for 2 h was triphasic, with half-lives of 3, 40, and 738 min. The longer half-life is presumed to be representative of the mobilization of toluene from adipose tissue, given the chemical's high lipophilicity. Brugnone (1985) reported half-lives of 1.8 and 29 min in vessel-rich tissue and muscle of humans, respectively, and 36 and 2.7 h in fat and vessel-poor tissues.

Metabolism and excretion of toluene are rapid, as indicated by recovery from behavioral deficits in rodents and rapid elimination from the brain following exposure (Gospe and Calaban 1988). ^{14}C-Labeled toluene decayed in an exponential manner from brain compartments of male Long-Evans rats, with negligible amounts detected at 4 h. At 15 min postexposure, concentrations were half of those at the end of exposure. Nonvolatile metabolites were not detected in the brain, and the CNS-depressant activity was attributed to toluene. Initial activity was highest in the lipid-rich medulla/pons followed by the mid-brain. However, elimination coefficients were not correlated with regional lipid content. The atmospheric concentration during the 10-min exposure was not specified. Radiolabeled toluene, injected into the antecubital vein, was cleared from the brain of baboons with a half-life of 10-20 min (Gerasimov et al. 2002).

Several factors influence rate and pathway of metabolism in humans (Nakajima et al. 1992; ATSDR 2000). The cytochrome P-450 isozymes responsible for toluene metabolism influence the relative production of benzyl alcohol, *o*-cresol, and *p*-cresol. There are two cytochrome P-450 isozymes that play major roles in the metabolism of toluene in rats: CYP2C11 and CYP2E1. The former has a high Km (metabolic rate constant) and becomes increasingly important with increasing exposure concentrations of toluene. The latter has a low Km and is induced by fasting and ethanol. CYP2B1 is induced by toluene concentrations as low as 500 ppm and is important for the formation of the genotoxic *o*-cresol (Wang et al. 1993). The action of these isozymes is influenced by factors, such as age, sex, and pregnancy (Nakajima eta l. 1992). Therefore, extrinsic and intrinsic factors can influence the relative amounts of the various urinary metabolites that are produced after toluene exposure.

Several studies indicated that measurement of hippuric acid in the urine could be used as an indicator of toluene exposure (Ogata et al. 1970; Nomiyama

and Nomiyama 1978; Hasegawa et al. 1983; Ogata 1984). However, measurement of hippuric acid may not be a good indicator of toluene exposure, as metabolism of other substances to hippuric acid may override the levels from toluene alone (NIOSH 1973; Stewart et al. 1975). When volunteers were exposed to deuterium-labeled toluene at 50 ppm and nonlabeled toluene at 50 ppm, there was little variation in labeled hippuric acid excretion among individuals (78% excreted after 20 h) (Lof et al. 1993). However, unlabeled hippuric-acid excretion varied widely among subjects and was about four times greater than what would have been generated by toluene exposure alone. In humans there are large variations in the amounts of toluene metabolites; therefore, monitoring of urinary metabolites can serve only as a qualitative marker for toluene exposure (Andersen et al. 1983; Hasegawa et al. 1983; Baelum et al. 1987).

The concentration of toluene in blood and tissues is proportional to the concentration in alveolar air, which in turn is proportional to the atmospheric concentration. Numerous investigators have reported on the exposure and alveolar concentration of toluene in relation to tissue content during controlled exposures in human subjects (Astrand et al. 1972; Gamberale and Hultengren 1972; Veulemans and Masschelein 1978; Carlsson 1982; Hjelm et al. 1988; Tardif et al. 1991) and animal models (Benignus et al. 1981, 1984; Bruckner and Peterson 1981a; Tardif et al. 1992; van Asperen et al. 2002). Nadeau et al. (2006) reported that toluene concentrations in alveolar air of human subjects exercising at 50100 W were 1.4- to 2.0-fold greater than from when exposures administered at rest. Several of the studies also measured toluene concentrations in the brain of rodents. With the exception of concentrations above 5,200 ppm in a study with the mouse (Bruckner and Peterson 1981a), all of the studies demonstrated a linear relationship between concentrations in both atmospheric and alveolar air and blood concentrations. At concentrations above 5,200 ppm, the metabolism of toluene may be saturated in the mouse. Although values appear comparable among some of the studies, differences in analytic techniques and the use of arterial rather than venous blood samples allow only general comparisons to be made.

Selected studies of toluene in human subjects and animal models are presented in Table 6-8 and presented graphically in Figure 6-2 (human studies) and Figure 6-3 (animal studies). The clinical studies represent different exposure situations, ranging from sedentary subjects to exercising subjects (Astrand et al. 1972; Lof et al. 1990; 1993) and to routine working conditions (von Oettingen et al. 1942). Steady-state may not have been reached for blood concentrations during the successive 20-min exposures in the study of Gamberale and Hultengren (1972). Where several studies involving the same species are available, there is relatively good agreement among peak blood concentrations. In general, for similar air concentrations, peak blood concentrations are inversely related to body size, being greatest in the mouse, followed by the rat and then the dog.

TABLE 6-8 Relationship between Ambient Air and Blood Concentrations of Toluene

Species	Exposure Duration	Air Concentration (ppm) (level of work)	Blood Concentration (mg/L)	Reference
Human	–	Background, general population	Up to 0.015	ACGIH 2001
Human	8 h (occupational)	40-54	0.41	Brugnone et al. 1986
Human	7 h	33	0.20	Tardif et al. 1997
Human	6.5 h 3.5 h	50 95	0.77 1.36	Tardif et al. 1991
Human	4.5 h	0 (control) 50	0.01 0.50	Muttray et al. 2005
Human	2 h	80 (rest) 80 (50 W)[b]	0.6 (mg/L, arterial)[a] 0.4 (mg/L, venous) 2.1 (mg/L, arterial) 1.2 (mg/L, venous)	Carlsson 1982
Human	4 h	53	0.28[c]; 0.52-0.64	Wallen et al. 1985
Human	4 h	80	0.47	Hjelm et al. 1988
Human	4 h	80 (no exercise)	0.52	Lof et al. 1990
Human	2 h	50 (exercise, 50 W)	0.92	Lof et al. 1993
Human 8 men 7 men	 4 h 4 h	 80 80	 1.17 0.98	Cherry et al. 1983; Waldron et al. 1983
Human	4 h (four 50-min exposures)	50 100 150	0.2 0.4 0.6	Veulemans and Masschelein 1978
Human	8 h 8 h	100 200	1.3 3.4	Angerer et al. 1980

(Continued)

TABLE 6-8 Continued

Species	Exposure Duration	Air Concentration (ppm) (level of work)	Blood Concentration (mg/L)	Reference
Human	6 h (occupational)	50-100	0.85-1.70	Neubert et al. 2001a
Human	20 min[d]	100	0.6	Gamberale and Hultengren 1972
	20 min	300	1.8	
	20 min	500	3.0	
	20 min	700	4.5	
Human	30, 60 min	100 (no exercise)	1.0	Astrand et al. 1972
	30 min	200 (no exercise)	2.0	
	30, 60 min	100 (exercise, 50 W)	2.3	
	30 min	200 (exercise, 50 W)	4.8	
Human	8 h (occupational)	Nonexposed	0.004	Foo et al. 1988
		32 (50 W)	0.56	
		65 (50 W)	0.99	
		86 (50 W)	1.3	
		115 (50 W)	1.5	
		132 (50 W)	1.9	
		196 (50 W)	2.6	
Dog	1 h	700	27	Hobara et al. 2000
	1 h	1,500	56	
	1 h	2,000	67	
Rat	1 h	2,000	100[b]	Oshiro et al. 2007

Rat	1 h		2,000 (sedentary)	31.5-42.8	Bushnell et al. 2007b;
			2,000 (active)	36.5-50.4	Kenyon et al. 2008
			2,000 (free fed)	25-31.7	
			2,000 (weight maintained)	16.7-28.1	
Rat	7 h		100	1.3	Korsak et al. 1991
Rat	5 h		75	0.7	Tardif et al. 1992
	5 h		150	2.7	
	5 h		225	5.1	
Rat	4 h		50	0.5	Haddad et al. 1999a
			100	1.3	
			200	5.0	
Rat	3 h		50	0.45	Benignus et al. 1984
	3 h		100	0.89	
	3 h		500	10.2	
	3 h		1,000	30.6	
Rat	2 h		1,000	58	Rees et al. 1985
	2 h		1,780	94	
	2 h		3,000	120	
Rat	4 h		125	2.5	Kishi et al. 1988
	4 h		250	7	
	4 h		500	17	
	4 h		1,000	27	
	4 h		2,000	70	
	4 h		4,000	120	
Rat	7.5 h		1,333	45	van Asperen et al. 2003;
	7.5 h		2,667	79	Lammers et al. 2005b
Mouse	2 h		1,300	97	Bruckner and Peterson 1981a
	2 h	2,600	147		
	3 h	4,000	200		
	2 h	5,200	242 2 h	10,400	315

[a] Blood concentrations were reported in mg/kg or µg/g.

[b] W, watts exercise (1 W = 4.2 calories/h).

[c] Concentrations reached a peak at 2.5 h and then decreased during the last 1.5 h. [d] These were successive exposures of 20 min each; steady-state may not have been reached at the higher concentrations.

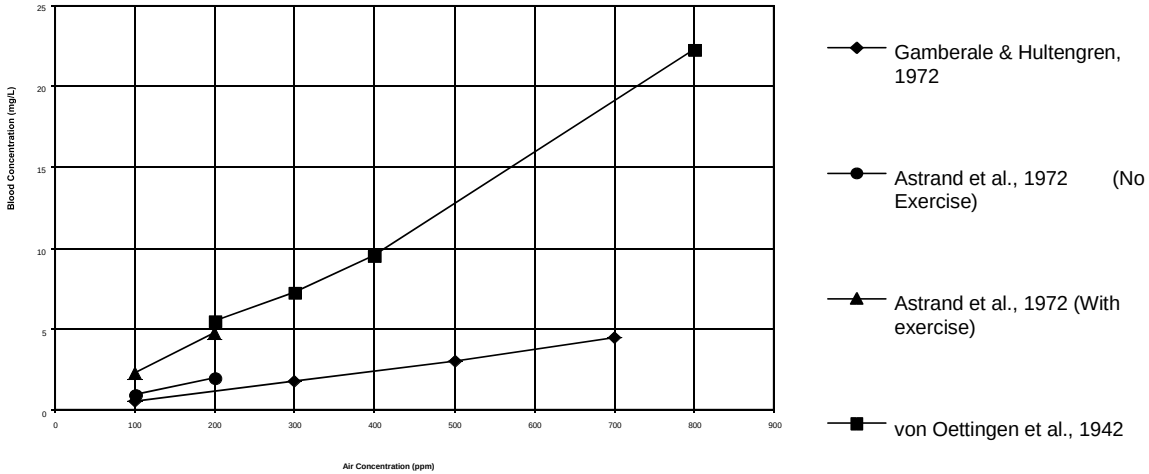

FIGURE 6-2 Relationship between air and blood concentrations of toluene in humans under different exposure conditions.

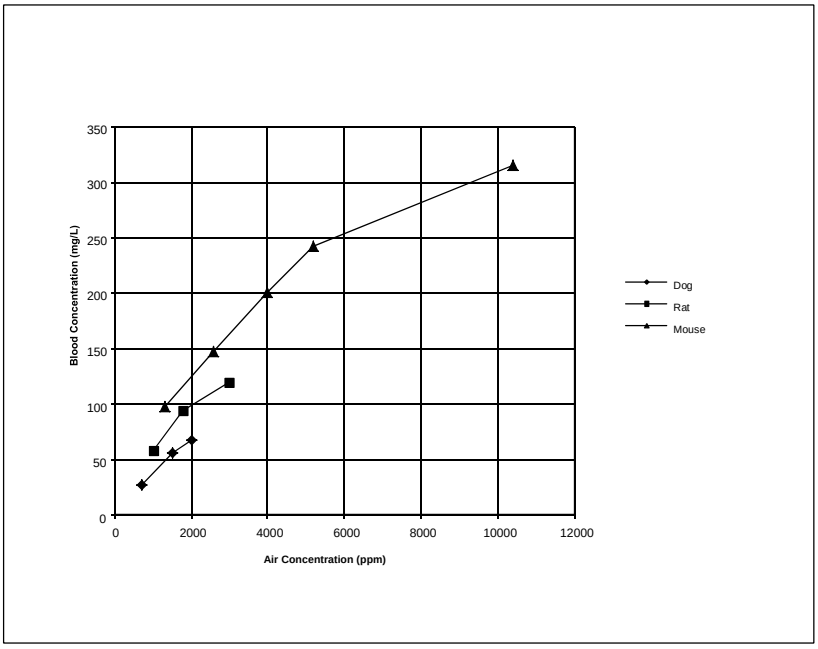

FIGURE 6-3 Relationship between air and blood concentrations of toluene in different animal species. Data for the dog, rat, and mouse are from studies by Hobara et al. (2000), Rees et al. (1985), and Bruckner and Peterson (1981a), respectively.

Using a single exposure concentration, Benignus et al. (1981) showed that blood and brain concentrations of toluene reach an asymptote fairly rapidly (Figure 6-4). The authors measured venous blood and brain concentrations of Long-Evans rats (gender unspecified) exposed to toluene at 575 ppm for 240 min. Animals were killed serially at 15, 30, 60, 120, and 240 min both during exposure and during a 240-min post-exposure period. The investigators fit the raw data to one-compartment, three-parameter models as shown in Figure 6-4. Blood and brain toluene concentrations achieved 95% of estimated asymptotes in 53 and 58 min, respectively. Estimated asymptotes were 10.5 ppm (mg/L) for venous blood and 18.0 ppm (mg/L) for brain. Blood and brain toluene concentrationss rose and fell at similar rates, although toluene in the brain fell slightly more rapidly than in the blood. The above value for brain concentration following exposure to toluene at 575 ppm is essentially the same as that of Carlsson and Lindqvist (1977), who measured a brain concentration of 15 µg/g (mg/L) in rats exposed at 550 ppm for 1 h. In studies of higher concentrations, 1,700, 3,400, and 5,100 ppm, Miyagawa et al. (1986) measured brain concentrations of approximately 120, 267, and 400 µg/g (mg/L), respectively (numbers read from

graph) in young male Sprague-Dawley rats. Concentrations were measured immediately after 4-h exposures.

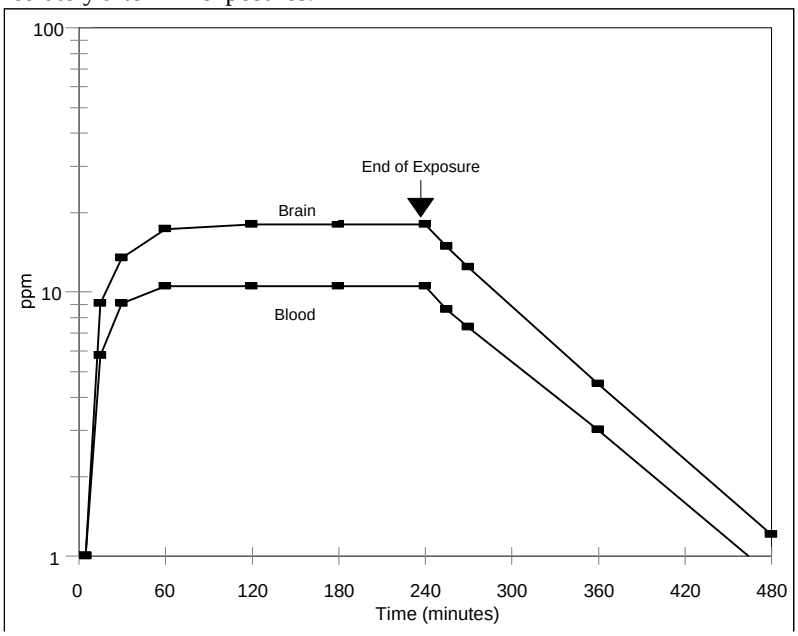

FIGURE 6-4 Toluene concentrations in the brain and venous blood of Long-Evans rats during and after exposure to toluene at 575 ppm for 4 h. (Blood concentrations of toluene given in ppm = mg/L.) Source: Adapted from Benignus et al. 1981.

A few studies reported blood toluene concentrations associated with coma in humans. Two workers admitted to the hospital in comas due to an accidental occupational exposure to mixed solvents had blood toluene concentrations of 823 and 1,122 µg/L at 36 h after the end of exposure (Brugnone et al. 1983). Respective alveolar air toluene concentrations were 53 and 38 µg/L. Calculated blood:air partition coefficients were 23 and 28, respectively. The decline in both compartments over the ensuing 5-day period allowed calculation of blood halflives of 27.1 and 17.1 h in the respective workers and alveolar half-lives of 20.8 and 17.5 h. The authors noted that these half-lives were for the decline of toluene in fat and other poorly perfused tissues, as the half-life from well-perfused tissues would be on the order of 2 min. Extrapolation to the end of exposure gave blood concentration of 6.2 and 8.4 mg/L, respectively.

Toluene concentrations have also been measured in fatalities, but measurements were taken several hours after exposure in most cases. In 1983, Paterson and Sarvesvaran reported a fatality involving a 16-year-old Caucasian male who was found dead with a plastic bag over his head. The trachea and

bronchi of the deceased contained inhaled stomach contents. His toluene blood concentration was 20.6 µg/mL, and the brain and liver concentrations were 297 and 89 µg/mg of tissue, respectively. The authors determined the cause of death to be toluene poisoning; they also stated that using a plastic bag to "concentrate" the vapors and direct inhalation from the bag contributed to the fatality. A painter who died following a fall had tissue concentrations of toluene in blood, lungs, liver, and brain of 48, 35, 65, and 80 µg/g, respectively (Takeichi et al. 1986). The authors stated that these concentrations were not definitely lethal, but were high enough to anesthetize the CNS.

Kojima and Kobayashi (1973) measured toluene in blood of rats that died during 30-50 min exposures at 20,000 ppm. Average toluene concentrations were 890 µg/g in the brain, 700 µg/g in the liver, and 330 µg/g in the blood. During additional exposures, no rats died when brain concentrations were less than 760 µg/g. No deaths occurred during a 120-min exposure at 5,000 ppm; average toluene concentrations in blood, liver, and brain during exposure were 220, 510, and 480 µg/g. Miyagawa et al. (1984) observed increased response rates of rats to a variable interval schedule-controlled operant task when the brain toluene concentrations were less than 200 µg/g and decreased response rates when brain toluene concentrations were between 200 and 350 µg/g. However, van Asperen et al. (2003) found that repeated high-dose spikes producing peak brain concentrations in rats up to 248 mg/L did not predict the level of behavioral impairment observed across different exposure scenarios.

Bruckner and Peterson (1981a) related the following blood concentrations in mice to states of CNS depression: 40-75 µg/g, ataxia; 75-125 µg/g, immobility in the absence of stimulation; 125-150 µg/g, hypnosis with arousal difficult; and >150 µg/g, unconsciousness. A good correlation between brain toluene concentrations and the extent of CNS depression was also found. Exposures were to toluene at 4,000 ppm for 3 h or 10,600 ppm for 10 min.

4.2. Mechanism of Toxicity

The most common consequence associated with toluene exposure at concentrations historically found in the workplace is CNS depression. CNS depression and narcosis are thought to involve the reversible interaction of toluene (not its metabolites) and lipid or protein components of nervous system membranes. Bruckner and Warren (2001) summarized present theories on mechanisms of action. These involve (1) a change in membrane fluidity, thereby altering intercellular communication and normal ion movements, (2) interaction with hydrophobic regions of proteins, thereby altering membrane-bound enzyme activity or receptor specificity, (3) enhancement of the neurotransmitter gammaaminobutyric acid ($GABA_A$) receptor function, and (4) activation of the dopaminergic system. Two mechanisms of toxicity have been proposed for CNS effects due to repeated exposure: 1) interaction of toluene with membrane proteins

and/or phospholipids in brain cells changes the activities of enzymes involved in the synthesis or degradation of neurotransmitters, which in turn may produce subtle neurologic effects, and (2) toluene may change the binding of neurotransmitters to membrane receptors (ATSDR 2000).

Intentional exposure to excessively high concentrations of toluene results in feelings of euphoria, which progress to lethargy and neurobehavioral deficits; these effects resemble those produced by anesthetics. Toluene is highly lipophilic and, as a nonpolar, planar molecule, can behave as an anesthetic by dissolving in the interior lipid matrix of a membrane. Increasing toluene concentration produces membrane expansion as well as changes in membrane structure and fluidity. Following an acute exposure, toluene diffuses out of the membrane, original integrity is regained, and functional characteristics can be restored (ATSDR 2000).

Renal toxicity with metabolic acidosis may be experienced at high concentrations of toluene. Distal renal tubular acidosis is an established consequence of toluene abuse and has been reported in numerous studies. In life-threatening cases, patients present with severe generalized muscle weakness, nausea and vomiting, and neuropsychiatric derangements (Streicher et al. 1981; Batlle et al. 1988; Marjot and McLeod 1989). The disorder results from the inability of the distal tubule of the nephron to secrete hydrogen ions through the active transport pathway of the collecting tubule of the kidney, resulting in metabolic acidosis with respiratory compensation and production of alkaline urine and hyperchloremia. The high anion gap of the blood may be due to the accumulation of the acidic metabolites of toluene, namely benzoic acid and hippuric acid.

The mechanism(s) of action at the molecular level for hearing loss and impairment of color vision are poorly understood (ATSDR 2000). In hearing loss, toluene exposure leads to a loss of outer hair cells in the ear. There may also be an effect on neural cell membranes. The postulated mechanism of action for color vision impairment involves toluene interference with dopaminergic mechanisms of retinal cells or demyelinization of optic nerve fibers.

4.3. Structure-Activity Relationships

No structure-activity issues have been identified with regard to toluene toxicity. In a summary statement based on the studies of benzene, toluene, and mixed xylenes, NTP (1990) states that methyl and dimethyl substitution on the benzene ring eliminates the carcinogenic activity in rodents. The toxicity of toluene resembles that of benzene except that toluene is devoid of benzene's chronic hematopoietic toxicity (Henderson 2001).

Because many alkylbenzenes have the same CNS depressant effect, similar to that of CNS-depressant drugs and ethanol, their relative potency as CNS depressants might be of relevance. In their study of the effects of toluene on the

functional observational battery in mice, Tegeris and Balster (1994) compared the effects of benzene and five alkylbenzenes with that of phenobarbital (5-40 mg/kg, intraperitoneal). The alkylbenzenes were toluene, ethylbenzene, propylbenzene, xylenes, and cumene. All exposures were to concentrations of 2,000, 4,000, or 8,000 ppm for 20 min. All agents decreased arousal, increased the ease of handling, decreased muscle tone, produced psychomotor impairment, and reduced reactivity to stimuli. At the two highest concentrations, the alkylbenzenes produced an anesthesia-like effect with loss of righting reflex (for phenobarbital, the loss of righting reflex occurred at 30 mg/kg). Both propylene and *m*-xylene required slightly higher concentrations to produce effects comparable to those of benzene, toluene, ethylbenzene, and cumene, although insufficient concentrations were studied to allow precise comparisons. The converse appears to be true for lethality. Where data on toluene and xylenes were available for the same species, LC_{50} values were slightly lower for xylene. For the mouse, the 6-h LC_{50} values for xylene isomers qwew 3,907-5,267 ppm, whereas the 6-h LC_{50} for toluene was 6,940 ppm (Bonnet et al. 1979).

4.4. Other Relevant Information

4.4.1. Interspecies Variability

Uptake of toluene by dogs (Hobara et al. 2000) appears to be more rapid and the blood concentrations attained slightly higher than those in several human studies (Figures 6-2 and 6-3). Uptake is somewhat greater in the rat than in humans, on the basis of blood: air partition coefficients and higher respiratory rate and cardiac output. The blood:air partition coefficient of 21.0 in rats is higher than that of humans (13.9) (Thrall et al. 2002).

Physiologically-based pharmacokinetic (PBPK) modeling was done in rats and humans (see Appendix C). PBPK modeling allows a comparison of the internal dose that is received in both species receiving identical external exposures. As can be seen in Figures 6-2 and 6-3, rats achieve higher blood toluene concentrations than humans. This is primarily due to the higher respiration rate and cardiac output, as well as a slightly higher blood:air partition coefficient in rats (13-21) (Sato and Nakajima 1979a; Gargas et al. 1989; Thrall et al. 2002; van Asperen et al. 2003) compared to humans (10-18; Thrall et al. 2002; Sato and Nakajima 1979a; Fiserova-Bergerova and Diaz 1986; Pierce et al. 1996a).

The interspecies factor is comprised of a pharmacodynamic component as well. A review of the data indicate little difference in interspecies sensitivity to toluene. Comparison of LC_{50} values for the rat and mouse shows that the mouse is slightly more sensitive than the rat. The 1-h LC_{50} in rats was 26,700 ppm (Pryor et al. 1978). In the mouse the 1-h LC_{50} was 19,018 ppm (confidence limits: 17,350-20,846 ppm) (Moser and Balster 1985). The sequelae of death was similar in both species with observations of lacrimation, hyperactivity, hypoactivity, lethargy,

and shallow respiration followed by death. The greater uptake of toluene in mice compared with rats, on the basis of respiratory rate and cardiac output, is offset to some degree by more rapid toluene metabolism by the mouse.

Neurotoxicity end points at the same concentration of toluene were also similar for rats and mice. For both species, 1,200 ppm was a chronic no-adverseeffect level (NTP 1990); for short-term exposures, motor activity was increased in rodents exposed at 1,000 ppm (see Tables 6-5 and 6-6). For rats and mice, 2,000 ppm may be the threshold for CNS depression, but a 50-min exposure at 2,000 ppm failed to produce an attention deficit in monkeys (Taylor and Evans 1985). At the same target tissue dose, humans may experience effects similar to those observed in animals, although it would take longer to attain the effects in humans due to a lower breathing rate per kilogram of body weight. In animals, death is preceded by increased activity, followed by narcosis, and is likely the result of depression of the CNS resulting in respiratory arrest. CNS depression with narcosis has also been observed in several accidental and intentional human exposures. Thus, nonlethal effects in both humans and animals are similar in nature and consist primarily of irritation and CNS effects at high concentrations of toluene.

Benignus et al. (2007) compared the acute neurotoxicity of toluene in rats and humans. A meta-analysis of dose-effect functions for variables such as choice reaction time in humans and reaction time in rats suggested that sensitivity to toluene is equivalent in humans and rats if both species performed behaviors that were controlled to the same extent.

4.4.2. Intraspecies Variability

Toluene produces CNS dysfunctions that are similar to those produced by other anesthetics (Bruckner and Warren 2001). Studies indicate that children, and particularly infants, are more resistant than adults to the effects 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 individuals of different ages has been extensively studied in the anesthesia literature where the concentrations of various anesthetic gases in the lungs which produce “anesthesia” (lack of movement) have been measured. Values are usually reported as the minimum alveolar concentration which produces lack of movement in 50% of persons exposed at that concentration. Minimum alveolar concentrations for several anesthetic gases have been measured as a function of age. The results consistently show a pattern with maximal sensitivity (lowest minimum alveolar concentration) in newborns, particularly premature infants, pregnant women, and the elderly. The least sensitive (highest minimum alveolar concentration values) occur in older infants, toddlers, and children compared with normal adults. The total range of sensitivity is 2-3 fold. On the basis of this

knowledge, it is not unreasonable to assume that the same 2-3 fold difference in sensitivity among individuals would apply for toluene.

In healthy adult male volunteers exposed to toluene at 40 ppm for 2 h (number of subjects not specified), blood toluene concentration differed by no more than 2-fold (Bessems et al. 2004). Small standard deviations in additional studies also indicate little inter-individual variation for a constant level of activity (Astrand et al. 1972; Carlsson 1982; Rahill et al. 1996). In one study, Pierce et al. (1999) reported an approximate 10-fold interindividual range in venous concentrations in two individuals exposed to toluene at 100 ppm for 2 h. The ventilation rate of these two subjects differed by a factor of two. A PBPK model indicates that there are no adult-children differences in tissue dose during inhalation (Pelekis et al. 2001).

4.4.3. Concentration-Response Relationship

The two primary effects of toluene exposure are irritation and CNS depression. Irritation is considered a threshold (concentration related) effect and therefore should not vary over time. CNS depression is also a concentrationrelated effect, with duration of exposure also a factor at higher exposures and short durations (less than 8 h). At low concentrations of 80 to 200 ppm, toluene approaches steady-state in the blood within 15-30 min (Astrand et al. 1972; Carlsson 1982). At higher concentrations, steady-state is approached in a concentration-related manner within one to several hours (Benignus et al. 1981; Gospe and Al-Bayati 1994). Storage would take place in lipid-rich tissues, but elimination is rapid. Once steady-state is reached, concentration is the prime determinant of toluene-induced CNS effects. Thus, concentrations that are not irritating or narcotic to humans within 30 min are assumed to have no greater effect with prolonged exposure.

Although blood concentrations can be used as a surrogate for brain concentrations, the target tissue for toluene, steady-state is not reached and there is much variability in the brain:blood ratio across durations at higher concentrations and the short durations relevant to AEGL derivation. As noted by Bushnell et al. (2007a), momentary brain concentration is most predictive of CNS effects. For higher exposure concentrations, PBPK modeling was used to determine human equivalent AEGL values from the animal data. PBPK modeling was used to calculate the internal dose (BrTC) in several studies with the rat. The general physiological and toxicokinetic (GPAT) human model for toluene was then used to determine the exposure concentrations in humans that yields the same concentration (Benignus et al. 2006). PBPK modeling allows a determination of the internal dose for the experimental species, and a determination of the external exposure which would lead to the same internal dose in the human. As can be seen in Figures 6-2 and 6-3, rats achieve higher blood toluene concentrations than humans. This is primarily due to the higher respiration rate and cardiac output, as well as a slightly higher blood:air partition coefficient in rodents.

4.4.4. Concurrent Exposure Issues

Toluene and a number of other volatile organic compounds are competitive metabolic inhibitors, as they are oxidized by some of the same P450 isozymes. The net effect is an increase in the blood and tissue (for example, brain) concentrations of each parent compound (despite some increase in exhalation) and an increase in the degree and duration of CNS depression. This may occur at "high concentrations," but at lower concentrations in both man (100 ppm) and rats (25 ppm), no significant interaction occurred (Ikeda 1974; Sato and Nakajima 1979b).

Tardif et al. (1992) reported that, compared with single 5-h exposures to toluene or xylene, the simultaneous exposure of adult male Sprague-Dawley rats to toluene (75, 150, and 225 ppm) and xylene (225, 150, and 75 ppm) resulted in interactive effects on metabolism. The interaction was evidenced by higher toluene concentrations in the blood and lower amounts of excreted metabolites over 24 h. There was some dependence of this effect on the ratio of the two chemicals. Furthermore, the effect was not observed at 50 ppm of toluene and 40 ppm xylene (Tardif et al. 1991).

Studies of toluene exposure (100 ppm) in combination with alcohol ingestion report delayed metabolism of toluene (Dossing et al. 1984), but there were no additive effects in neurobehavioral tests (4-h exposure at 80 ppm) (Cherry et al. 1983).

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Twenty controlled human studies that describe the threshold for irritation and CNS effects from acute exposures to toluene or toluene concentrate have been conducted (Table 6-3). The effects in these studies include slight sensory irritation, accompanied by headache in some cases, subtle impairment on some sensitive cognitive-function tasks, and occasional slight dizziness. The more recent studies involved exposure durations of up to 4 h at 80 ppm, 7.5 h at 100 ppm, and 7 h at 200 ppm. Although slight sensory irritation was reported in subjects exposed to toluene at 80-200 ppm in some studies (Andersen et al. 1983; Baelum et al. 1985, 1990; Echeverria et al. 1989, 1991), these concentrations were not irritating in other studies (Stewart et al. 1975; Cherry et al. 1983; Olson et al. 1985; Rahill et al. 1996) and the exposures were generally considered acceptable (no annoyance). True sensory irritation from toluene was reported at concentrations of 20,000 ppm or higher in human studies (Cometto-Muniz and Cain 1995; Abraham et al. 1996), but could not be determined in the mouse (Nielsen and Alarie 1982). No differences in performance on neurobehavioral tests were found in some studies,

and others found only subtle differences that indicated slight reductions in alertness (Ogata et al. 1970; Gamberale and Hultengren 1972; Stewart et al. 1975; Winneke 1982; Andersen et al. 1983; Cherry et al. 1983; Dick et al. 1984; Olson et al. 1985; Baelum et al. 1985, 1990; Echeverria et al. 1989, 1991; Rahill et al. 1996). There were no biologically significant pulmonary or cardiovascular effects (Astrand et al. 1972; Gamberale and Hultengren 1972; Suzuki 1973) and no indications of renal damage (Nielsen et al. 1985). The studies by Rahill et al. (1996), Astrand et al. (1972), and Baelum et al. (1990) found that exercise doubled the uptake of toluene by blood. The study by Stewart et al. (1975) involved repeated exposure to toluene, and found no greater effects over time. Baelum et al. (1990) also tested concentrations that ranged between 50 and 300 ppm (repeated 14 times during a 7-h exposure) with a TWA of 100 ppm; the subjects exercised during the peak exposures at 300 ppm. Gamberale and Hultengren (1972) tested higher concentrations of toluene, but the exposure durations were relatively short and toluene was delivered via breathing tube. Concentrations of toluene above 300 ppm were associated with subtle differences in the speed of reacting to a stimulus or completing a task. For example, during a 20-min exposure at 700 ppm, it took subjects approximately 30 sec longer than controls to match three-digit numbers in 60 columns with numbers appearing at the top of the column (the test was two pages in length).

In metabolism studies, subjects were routinely exposed to toluene at 78200 ppm for several hours, with and without exercise (Nomiyama and Nomiyama 1978; Veulemans and Masschelein 1978; Carlsson 1982; Dossing et al. 1984; Wallen et al. 1985; Hjelm et al. 1988). These studies did not evaluate subjective effects, because they were undertaken to study the toxicodynamics and toxicokinetics of toluene in people exposed in the workplace.

Occupational-monitoring studies indicate that workers presumed to be healthy have been exposed to toluene at a TWA of 100 ppm or higher without adverse effects. In a comprehensive, well-conducted occupational-monitoring study involving more than 1,000 workers, Neubert et al. (2001a) failed to find alterations in motor performance or increased subjective complaints in workers exposed to toluene at TWA concentrations of 50-100 ppm compared with matched control groups. Workers exposed chronically to toluene at concentrations greater than 100 ppm (66-800 ppm) did not have greater attention deficits or sensory symptoms in neurologic tests than those exposed acutely (Foo et al. 1990; Zavalic et al. 1998; Neubert et al. 2001a). Irritation of the conjunctiva and upper respiratory tract was found in only one of 11 workers exposed at 200-800 ppm (Parmeggiani and Sassi 1954). Occupational exposures to toluene at concentrations up to 300 ppm (Bauchinger et al. 1982), 350 ppm (Ovrum et al. 1978), and 467 ppm (Deschamps et al. 2001) have also been reported.

5.2. Animal Data Relevant to AEGL-1

Few animal studies of end points relevant to AEGL-1 values for toluene were found. Toluene at 1,200 ppm was a NOAEL for overt behavior changes in rodents exposed chronically (NTP 1990). Subtle changes in rodent behavior are not possible to observe, and the effects on rat and mouse behavior described in Tables 6-5 and 6-6, respectively, are sometimes conflicting. Motor activity either remained unchanged or increased at concentrations below 1,000 ppm; this stimulatory effect was accompanied by either an increase or decrease in positive responses in subtle neurobehavioral tests.

5.3. Derivation of AEGL-1 Values

Multiple clinical, occupational-monitoring, and metabolism studies found effects below the definition of the AEGL-1 (notable discomfort). It is not feasible to model notable discomfort, so AEGL-1 values were based on the preponderance of data from clinical and occupational studies and from metabolism studies with human subjects that indicated that an 8-h exposure to toluene at 200 ppm is a NOAEL for notable discomfort, but elicited subjective, low-severity, nonsensory effects in some studies. More than 300 individuals were involved in the clinical studies summarized in Table 6-3. Several thousand workers were surveyed in the occupational-monitoring studies. Although these populations are presumed to be composed of healthy individuals, they represent a broad spectrum of uptake rates (sedentary, working, and exercise conditions) and individual differences in metabolism rates (Gamberale and Hultengren 1972; Veulemans and Masschelein 1978; Brugnone et al. 1986; Hjelm et al. 1988). Although slight respiratory irritation was reported at 100 and 200 ppm in several studies, toluene is not a respiratory irritant as evidenced by the high RD_{50} value of 5,300 ppm (Nielsen and Alarie 1982). In addition, the severity of the irritation and the neurobehavioral effects reported in these studies was generally below the definition of AEGL-1.

The highest NOAELs for notable discomfort were 200 ppm for 60 min (Astrand et al. 1972), 300 ppm for 15 min (Baelum et al. 1990), and 700 ppm for 20 min (Gamberale and Hultengren 1972). NOAELs for nonsensory (neurobehavioral) effects were 100 ppm for 4 h (Dick et al. 1984), 6 h (Rahill et al. 1996), and 6.5 h (Baelum et al. 1985, 1990; Nielsen et al. 1985); 150 ppm for 7 h (Echeverria et al. 1989, 1991); and 200 ppm for 3 h (Ogata et al. 1970). Exercise during the studies of Astrand et al. (1972) and Baelum et al. (1990) takes into account the increased uptake that may occur during an emergency situation. Although a steady-state in blood and brain toluene concentrations would be approached but not attained during the 15-and 20-min exposures, the blood concentration of toluene has been shown to increase approximately two-fold with moderate exercise of 50 W (Astrand et al. 1972). Therefore, the preponderance of data indicates that an 8-h exposure to toluene at 200 ppm is a NOAEL for AEGL-1 effects; however, some subjective neurobehavioral effects have been reported. Although there was no notable discomfort and only mild irritation (effects

expected to be concentration dependent and not subject to changes in activity level), headaches (potentially related to CNS effects), reports of dizziness, and nonmeasurable neurologic effects have been reported at 100-200 ppm in controlled human studies (von Oettingen et al. 1942; Gamberale and Hultengren 1972; Andersen et al. 1983). Neurologic effects would be expected to be affected by an increase in activity level, leading to higher concentrations of toluene in the brain. As noted earlier, moderate physical activity may double the blood concentration of toluene.

Empirical data as well as pharmacokinetic modeling in humans and rodents indicate that venous-blood and brain concentrations of toluene rapidly increase during the first 15-20 min of exposure, followed by relatively modest increases in blood concentrations with continuing exposure (Gamberale and Hultengren 1972; Tardif et al. 1993, 1995). At low concentrations, toluene reaches an asymptote in the blood within 20-30 min (Gamberale and Hultengren 1972; Carlsson 1982). Although storage of toluene would take place in lipid-rich tissues (including those of the brain), elimination is also rapid. On the basis of the range of alveolar concentrations among humans exposed to anesthetic gases (see Section 4.4.2), an uncertainty factor of 3 for intraspecies variability was applied to derive a value of 67 ppm. That concentration was used for all of the AEGL durations, because a steady-state of at 67 ppm is reach fairly rapidly. The AEGL-1 values for toluene are presented in Table 6-9, and the calculations in Appendix A. The relationship between the AEGL-1 values and human exposures is shown in Appendix B.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

In humans and animals, the primary effect associated with inhalation of "high concentrations" is CNS depression. Few studies of controlled or accidental exposures to toluene evaluated CNS depression of a severity that would inhibit the ability to escape. Gamberale and Hultengren (1972) exposed volunteers to toluene at 700 ppm for 20 min, following successive 20-min exposures at 100, 300, and 500 ppm (total exposure duration 85 min). The work by Benignus et al. (2011) shows a useful comparative analysis equating decrements in neurologic functioning associated with blood ethanol levels across exposures to a number of volatile solvents, including toluene.

There was one case report of accidental human exposure to toluene, which was appropriate as a basis for deriving AEGL-2 values (Meulenbelt et al. 1990). Two men used toluene to remove excess glue from tiles in the bottom of a swimming pool. The men were barely conscious when they were found; they were confused and unable to walk. They also suffered paresis, ocular irritation, amnesia, and had increased anion gaps, presumably from the onset of distal renal tubular acidosis from the metabolites, hippuric and benzoic acid. The toluene

concentration measured above the site several hours later was greater than 1,842 ppm, although the victims were likely exposed at higher concentrations at the bottom of the pool. The duration of exposure was approximately 2.5 h.

6.2. Animal Data Relevant to AEGL-2

Except for increased locomotor activity, toluene concentrations below 1,000 ppm have little or no effect on gross manifestations of animal behavior (NRC 1981; WHO 1987). At concentration of 2,000 ppm lower, increased motor activity and an increased rate of responding in neurobehavioral tests were found in rodents (Glowa 1981; De Ceaurriz et al. 1983; Bushnell et al. 1985; Miyagawa et al. 1986; Hinman 1987; Kishi et al. 1988; Wada et al. 1989; Wood and

TABLE 6-9 AEGL-1 Values for Toluene

10 min	30 min	1 h	4 h	8 h
67 ppm (250 mg/m^3)	67 ppm 250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)

Cox 1995) and monkeys (Taylor and Evans 1985). Higher concentrations of toluene suppress activity. Rats exposed to toluene at 2,400 ppm for 70 min performed more poorly on a signal detection task than controls (Oshiro and Bushnell 2004). The rats were described as sleepy but arousable. Adult female macaque monkeys were affected little by a 50-min exposure to toluene at 2,000 ppm or lower; an attention deficit was found during a 50-min exposure at 3,000 ppm, and failure to respond occurred during the second half of a 50-min exposure at 4,500 ppm (presumably indicating narcosis) (Taylor and Evans 1985). The NOAEL for clinical signs, survival, and carcinogenicity in mice and rats after chronic inhalation exposure to toluene is 1,200 ppm (NTP 1990). Exposures in the NTP study were for 6.5 h/day, 5 days/week for 2 years.

6.3. Derivation of AEGL-2 Values

AEGL-2 values for toluene are based on a notable increase in reaction time. The point of departure was a NOAEL of 1,600 ppm based on doubling of reaction time in Long-Evans rats exposed for 34 min (Bushnell et al, 2007a). This point of departure is supported by modeling that shows that a similar magnitude of behavioral impairment is caused by oral ingestion of ethanol to the point of legal intoxication (Benignus et al. 2007, 2011). The CNS effects observed following toluene exposure are assumed to be directly related to concentrations of the parent chemical in the brain at the time the effects were measured. Therefore, the BrTC

at the 34-min exposure would be expected to provide an internal dose correlating with the NOAEL.

The PBPK model of Kenyon et al. (2008) was used to calculate the internal dose (BrTC) in the rat. An interspecies uncertainty factor of 1 was applied because pharmacokinetic modeling eliminated the toxicokinetic component of the uncertainty factor, and the pharmacodynamic component was assigned a value of 1 because similar effects (CNS depression) were observed in humans and animals. An intraspecies uncertainty factor of 3 was applied because the minimum alveolar concentration (lowest concentration causing an anesthetic effect) for volatile anesthetics should not vary by more than 2- to 3-fold among humans (see Section 4.4.2).

The GPAT model developed by Benignus et al. (2006) is a human wholebody differential equation-based model for simulating the function of the various organs in response to realistic situations, such as exercise, environment, and diet. The environmental aspects include temperature, humidity, and, in this application, toluene uptake and elimination for each organ. Thus, toluene uptake and elimination under various exposures was estimated for each organ, most notably the brain, and for various exercise levels. In addition, estimates were made of the exposure concentrations that would lead to specific organ concentrations (BrTC) in humans based on output from the Kenyon et al. (2008) rat PBPK model. The target internal dose metric in humans (human BrTC) was calculated by dividing the rat BrTC by the total uncertainty factor of 3. The human GPAT model (Benignus et al. 2006) was then used to determine the equivalent exposure concentration that yields the human BrTC at each of the AEGL exposure durations.

Similar types of neurobehavioral effects are caused by ethanol intoxication and have been well documented. Comparisons of the effects caused by the modeled levels of toluene and similar effects caused by ethanol intoxication (using blood ethanol concentration as the indicator) have been included in Appendix C (Table C-4), Appendix D, and in the paper by Benignus et al. (2011) to further support the approach taken in deriving the AEGL-2 values.

Time-scaling calculations are presented in Appendix A and the PBPK modeling methods are explained in Appendix C. AEGL-2 values for toluene are presented in Table 6-10, and are shown graphically in Appendix B.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Human data on toluene concentrations that are the threshold for lethality are sparse. In a shipboard accident, workers lost consciousness after being exposed to estimated concentrations of toluene that ranged from 5,000 to 30,000 ppm (Longley et al. 1967). The exposure was at least 75 min in duration. Because

toluene is heavier than air, the higher concentration was most likely near the floor where a kneeling worker rapidly lost consciousness. All workers recovered. Press and Done (1967) estimate the concentration of toluene achieved when inhaling directly from a paper bag containing gauze soaked with toluene (abuse situation) at 10,000 ppm. One of the authors inhaled from the bag for 5 min, and reported dizziness, blurred vision, roaring and buzzing in the ears, and slurred speech.

7.2. Animal Data Relevant to AEGL-3

On the basis of LC_{50} values, the mouse is slightly more sensitive to the effects of toluene than the rat. LC_{50} values for the mouse for 10, 30, and 60 min are 38,465, 21,872, and 19,018 ppm, respectively (Moser and Balster 1985). The 3-h LC_{50} was 8,600 ppm (Bruckner and Peterson 1981a). A 6-h LC_{50} of 6,940 ppm was calculated by Bonnet et al. (1979) and a 7-h LC_{50} of 5,320 was calculated by Svirbely et al. (1943). For the rat, LC_{50} values ranged from 26,700 ppm for 1 h to 12,500 ppm for 2-2.5 h (Pryor et al. 1978; Kojima and Kobayashi 1973). Death was caused by severe CNS depression and respiratory failure.

Data were also available on the highest concentrations of toluene that did not result in lethality. No deaths occurred in mice exposed to toluene for 20 min at 12,000 ppm (Bruckner and Peterson 1981a), in rats exposed for 2 h at 5,000 or 6,250 ppm (Kojima and Kobayashi 1973; Mullin and Krivanek 1982), or in rats exposed for 4 h at 6,000 ppm (Wada et al. 1989). Mice exposed at 6,000 ppm for 30 min/day, 5 days/week for 7 weeks and that were deprived of food survived the exposures in apparent good health (Moser and Balster 1981). Additionally, mice and rats tolerated toluene at 1,200 ppm for 2 years without an effect on mortality (NTP 1990).

7.3. Derivation of AEGL-3 Values

The AEGL-3 values are based on a NOAEL for lethality in the rat. A 2-h exposure at 6,250 ppm was not lethal but produced prostration in rats (Mullin and Krivanek 1982). CNS effects observed following toluene exposure were assumed to be directly related to concentration of parent chemical in the brain at the time effects were observed. Therefore, the PBPK model of Kenyon et al. (2008) was used to calculate the BrTC in the rat. An interspecies uncertainty factor of 1 was applied because pharmacokinetic modeling eliminated the toxicokinetic component of the uncertainty factor, and the pharmacodynamic component was assigned a factor of 1 because similar effects (CNS depression) were observed in humans and animals. An intraspecies uncertainty factor of 3 was applied to account for intraindividual variability, as was done for the AEGL-2. A human GPAT model (Benignus et al. 2006) was used to determine the equivalent exposure concentration in humans for each of the AEGL exposure durations.

Time-scaling calculations are presented in Appendix A, and the PBPK modeling methods are explained in Appendix C. AEGL-3 values are presented in Table 6-11, and shown graphically in Appendix B.

TABLE 6-10 AEGL-2 Values for Toluene

10 min	30 min	1 h	4 h	8 h
1,400 ppm[a] (5,300 mg/m^3)	760 ppm (2,900 mg/m^3)	560 ppm (2,100 mg/m^3)	310 ppm (1,200 mg/m^3)	250 ppm (940 mg/m^3)

[a] Concentration is one-tenth of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, safety considerations against the hazard of explosion must be taken into account.

TABLE 6-11 AELG-3 Values for Toluene

10 min	30 min	1 h	4 h	8 h
–[a]	5,200 ppm[b] (20,000 mg/m^3)	3,700 ppm[b] (14,000 mg/m^3)	1,800 ppm[b] (6800 mg/m^3)	1,400 ppm[b] (5300 mg/m^3)

[a] The 10-min AEGL-3 value of 10,000 ppm (38,000 mg/m^3) is higher than 50% of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, extreme safety considerations against the hazard of explosion must be taken into account. [b] Concentration is one-tenth or more of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, safety considerations against the hazard of explosion must be taken into account.

Workers lost consciousness after being accidentally exposed to toluene at an estimated concentration of 5,000 ppm or greater for an undefined period of time (Longley et al. 1967). In rodent studies, concentrations of 5,000 ppm for 2 h (Kojima and Kobayashi 1973), 12,000 ppm for 20 min (Bruckner and Peterson 1981a), and 6,000 ppm for 30 min/day, 5 day/week for 7 weeks (Moser and Balster 1981) were all nonlethal.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity End Points

The AEGL values for toluene are presented in Table 6-12.

8.2. Comparison with Other Standards and Criteria

Standards and guidance levels for workplace and community exposures to toluene are presented in Table 6-13. The Occupational Health and Safety

Administration recommends a 10-min maximum exposure of 500 ppm. The National Institute for Occupational Safety and Health's immediately dangerous to life or health (IDLH) value is also 500 ppm. The IDLH is based on the human data of Gamberale and Hultengren (1972), von Oettingen et al. (1942), and Wilson (1943), and was established at a concentration lower than both the 30-min AEGL-2 and AEGL-3 values. The IDLH is based on a weight-of-evidence approach from human data only, with the final value based on a consensus from a panel of experts. No quantitative analysis or application of PBPK models to approximate the human exposure which would lead to a NOAEL in the rat was used to determine the IDLH concentration whereas a quantitative approach was used in the development of the AEGL-2 and AEGL-3 values. The emergency response planning guideline (ERPG) values of the American Industrial Hygiene Association (AIHA 2013) are lower than the AEGL values. The ERPG-1 is based on controlled human studies (von Oettingen et al. 1942; Gamberale and Hultengren 1972; Andersen et al. 1983) in which exposure at 100 ppm produced mild symptoms, such as fatigue, drowsiness, headache, dizziness, and feeling of intoxication without measurable neurotoxic effects; these studies were considered in the derivation of the AEGL-1 values in the context of 20 relevant human studies. The final resulting AEGL-1 value of 67 ppm was deemed protective for these low-level, subjective effects. The ERPG-2 was based on controlled human studies in which exposure at 300 ppm for 8 h did not result in muscular weakness or incoordination (von Oettingen et al. 1942). This is an old study and was not considered for AEGL development. The ERPG-3 was based on the 1-h LC_{50} of 26,700 ppm in rats (Pryor et al. 1978), divided by approximately 20 and the reported loss of consciousness in humans exposed at 5,000 ppm for a few minutes (Longley et al. 1967). The National Research Council (NRC) 1-h emergency exposure guidance level for toluene is 200 ppm for workplace conditions (NRC 2008).

TABLE 6-12 AEGL Values for Toluene

Classification	10 min	30 min	1 h	4 h	8 h
AEGL-1 (nondisabling)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)
AEGL-2 (disabling)	1,400 ppm[a] (5,300 mg/m^3)	760 ppm (2,900 mg/m^3)	560 ppm (2,100 mg/m^3)	310 ppm (1,200 mg/m^3)	250 ppm (940 mg/m^3)
AEGL-3 (lethal)	–[b]	5,200 ppm[a] 20,000 mg/m^3)	3,700 ppm[a] (14,000 mg/m^3)	1,800 ppm[a] (6,800 mg/m^3)	1,400 ppm[a] (5300 mg/m^3)

[a] Concentration is one-tenth or more of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, safety considerations against the hazard of explosion must be taken into account.

[b] The 10-min AEGL-3 value of 10,000 ppm (38,000 mg/m^3) is higher than 50% of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

TABLE 6-13 Standards and Guidelines for Toluene

	Exposure Duration					
Guideline	10 min	15 min	30 min	1 h	4 h	8 h
AEGL-1	67 ppm	–	67 ppm	67 ppm	67 ppm	67 ppm
AEGL-2	1,400 ppm[a]	–	760 ppm	560 ppm	310 ppm	250 ppm
AEGL-3	–[b]	–	5,200 ppm[a]	3,700 ppm[a]	1,800 ppm[a]	1,400 ppm[a]
ERPG-1 (AIHA)[c]	–	–	–	50 ppm	–	–
ERPG-2 (AIHA)	–	–	–	300 ppm	–	–
ERPG-3 (AIHA)	–	–	–	1,000 ppm	–	–
EEGL (NRC)[d]	–	–	–	200 ppm	–	–
SMAC (NRC)[e]	–	–	–	16 ppm	–	–
IDLH (NIOSH)[f]	–	–	500 ppm	–	–	–
TLV-TWA (ACGIH)[g]	–	–	–	–	–	50 ppm
PEL-TWA (OSHA)[h]	–	–	–	–	–	200 ppm
REL-TWA (NIOSH)[i]	–	–	–	–	–	100 ppm
REL-STEL (NIOSH)[j]	–	150 ppm	–	–	–	–
PEL-C (OSHA)[k]	300 ppm	300 ppm	300 ppm	300 ppm	300 ppm	300 ppm
PEL-peak (OSHA)[l]	500 ppm	–	–	–	–	–
MAK (Germany)[m]	–	–	–	–	–	50 ppm
MAK peak exposure (Germany)[n]	–	–	250 ppm	–	–	–
MAC (The Netherlands)[o]	–	–	–	–	–	40 ppm

[a] Concentration is one-tenth or more of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, safety considerations against the hazard of explosion must be taken into account.

[b] The 10-min AEGL-3 value of 10,000 ppm (38,000 mg/m^3) is higher than 50% of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

[c]

ERPG (emergency response planning guidelines, American Industrial Hygiene Association) (AIHA 2013).

ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for toluene is based on controlled human studies (von Oettingen et al. 1942; Gamberale and Hultengren 1972; Andersen et al. 1983) in which exposure at 100 ppm produced mild symptoms, such as fatigue, drowsiness, headache, dizziness, and feeling of intoxication without neurotoxic effects.

ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-2 for toluene was based on controlled human studies in which exposure at 300 ppm for 8 h did not result in muscular weakness or incoordination (von Oettingen et al. 1942).

ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to 1 h without experiencing or developing lifethreatening health effects. The ERPG-3 for toluene was based on the LC_{50} in rats (Pryor et al. 1978), divided by approximately 20, and the reported loss of consciousness in humans exposed at 5,000 ppm for a few minutes (Longley et al. 1967).

d

EEGL (emergency exposure guidance levels, National Research Council) (NRC 2008). The EEGL is the concentration of a contaminant that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects, and long-term or chronic injury.

e

SMAC (spacecraft maximum allowable concentration, National Research Council) (NRC 2008). SMACs are intended to provide guidance on chemical exposures during normal operations of spacecraft, as well as emergency situations. The 1-h SMAC is a concentration of an airborne substance that will not compromise the performance of specific tasks by astronauts during emergency conditions or cause serious or permanent toxic effects. Such exposures may cause reversible effects, such as dermal or ocular irritation, but they are not expected to impair judgment or interfere with proper responses to emergencies.

f

IDLH (immediately dangerous to life or health, National Institute for Occupational Safety and Health) (NIOSH 1994) represents the maximum concentration from which one could escape within 30 min without any escape-impairing symptoms, or any irreversible health effects. The IDLH for toluene is based on the human studies of Gamberale and Hultengren (1972), von Oettingen et al. (1942) and Wilson (1943).

g

TLV-TWA (threshold limit value – time-weighted average, American Conference of Governmental Industrial Hygienists) (ACGIH 2005) 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. There is a skin notation for the TLV for toluene. *h*

PEL-TWA (permissible exposure limit – time-weighted average, Occupational Health and Safety Administration) (29 CFR 1910.1000 [2006]) is a time-weighted average concentration that must not be exceeded during any 8-h workshift of a 40-h workweek.

i

REL-TWA (recommended exposure limit – time-weighted average, National Institute for Occupational Safety and Health) (NIOSH 2011) is a time-weighted average concentration for up to a 10-h workday during a 40-h workweek.

[h] REL-STEL (recommended exposure limit – short-term exposure limit, National Institute for Occupational Safety and Health) (NIOSH 2011) is a 15-min time-weighted average exposure that should not be exceeded at any time during a workday.

[j] PEL-C (permissible exposure limit – ceiling, Occupational Health and Safety Administration) (29 CFR 1910.1000 [2006]) is a ceiling value that should not be exceeded during any part of the workday. If instantaneous monitoring is not feasible, the ceiling must be assessed as a 15-min time-weighted average exposure.

[l] PEL-peak (permissible exposure limit – peak, Occupational Health and Safety Administration) (29 CFR 1910.1000 [2006]) is the acceptable 10-min maximum peak above the acceptable ceiling value.

[m] MAK (maximale arbeitsplatzkonzentration [maximum workplace concentration]) (Deutsche Forschungsgemeinschaft [German Research Association] (DFG 1999) is defined analogous to the ACGIH TLV-TWA.

[n] MAK spitzenbegrenzung (peak limit [Category II, 2], Deutsche Forschungsgemeinschaft [German Research Association]) (DFG 1999) is the maximum average concentration to which workers can be exposed for a period up to 30 min with no more than two excursions per work shift; total exposure may not exceed 8-h MAK.

[o] MAC (maximaal aanvaarde concentratie [maximal accepted concentration], Dutch Expert Committee for Occupational Standards, The Netherlands (MSZW 2004) is defined analogous to the ACGIH TLV-TWA.

Exposure limits for chronic exposures are lower than for emergency guidelines. The American Conference of Governmental Industrial Hygienists (ACGIH 2005) occupational exposure limit for toluene is 50 ppm, as is the German MAK (German Research Association (DFG 1999). The Dutch MAC is 40 ppm (MSZW 2004). The 8-h AEGL-1 for toluene is 200 ppm. The previous ACGIH TWA value of 200 ppm was lowered in 1991 on the basis of slight irritation at 100 ppm, described in the studies of Andersen et al. (1983), Baelum et al (1985), Wilson (1943), and Echeverria et al. (1989). The AEGL-1 value is higher than the TLV because slight irritation is acceptable under acute (once-in-a-lifetime) conditions. Furthermore, it is unlikely that an intolerable level of annoyance of sensory irritation was reached in the Andersen et al. (1983) study, given the inability to attain an RD_{50} (Nielsen and Alarie 1982).

The NRC (2008) spacecraft maximum allowable concentration for toluene is 16 ppm for 1 and 24 h. The SMAC values were based on a single study (Andersen et al. 1983), rather than the preponderance of the evidence from 20 published studies.

8.3. Data Adequacy and Research Needs

Because toluene is a commonly used solvent, its effects on humans have been extensively studied. Numerous controlled studies with human subjects that addressed effects meeting the definition of the AEGL-1 were available. The data base of neurotoxicity studies with animals is extensive, and the supporting animal data were in good agreement with the AEGL values based on the human studies. Toluene is fatal to humans only after exposure at extremely high concentrations. Although the animal data base on lethality was limited to rodents (rats and mice), the agreement between these two species was good.

The anesthetic effects and metabolism of toluene are well documented and well understood. Although specific sensitive populations were not identified, the mechanism of action of CNS depression is the same for all mammalian species, and the concentration at which this effect occurs after toluene inhalation does not differ greatly among individuals.

Although an abundance of empirical data exists concerning the toxicity of toluene in several species (including humans), there is a lack of good concentration-effect data for the exposure-time relationships. This data gap is particularly prominent with respect to human exposures. While there are several wellconducted, controlled, chamber studies involving human subjects, the exposure concentrations are limited to those that produce very little if any impairment or anesthetic effects in humans. Therefore animal data extrapolated to humans via PBPK modeling were used to calculate exposure-duration-specific AEGL values.

9. REFERENCES

Abbate, C., C. Giogianni, F. Munao, and R. Brecciaroli. 1993. Neurotoxicity induced by exposure to toluene: An electrophysiologic study. Int. Arch. Occup. Environ. Health 64(6):389-392.

Abraham, M.H., J. Andonian-Haftvan, J. Enrique Cometto-Muniz, and W.S. Cain. 1996. An analysis of nasal irritation thresholds using a new solvation equation. Fundam. Appl. Toxicol. 31(1):71-76.

ACGIH (American Conference of Governmental Industrial Hygienists, Inc). 2001. Toluene (CAS No. 108-88-3). Recommended BEI. American Conference of Governmental Industrial Hygienists, Inc., Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists, Inc). 2005. Toluene. Threshold Limit Values for Chemical Substances and Physical Agents Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Inc., Cincinnati, OH.

AIHA (American Industrial Hygiene Association). 1989. Odor Thresholds for Chemicals with Established Occupational Health Standards. Fairfax, VA: AIHA.

AIHA (American Industrial Hygiene Association). 2013. Current ERPG Values. 2013 ERPG/WEEL Handbook. American Industrial Hygiene Association Guideline Foundation, Fairfax, VA [online]. Available: https://www.aiha.org/get-involved/AI

HAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2013ERPGValues.pdf [accessed Mar. 25, 2014].

Ali, N., and R. Tardif. 1999. Toxicokinetic modeling of the combined exposure to toluene and n-hexane in rats and humans. J. Occup. Health 41(2):95-103.

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3(6):272-289.

Andersen, I., G.R. Lundqvist, L. Molhave, O.F. Pedersen, D.F. Proctor, M. Vaeth, and D.P. Wyon. 1983. Human response to controlled levels of toluene in 6-h exposures. Scand. J. Work Environ. Health 9(5):405-418.

Anderson, D., and J.A. Styles. 1978. An evaluation of 6 short-term tests for detecting organic chemical carcinogens. The bacterial mutation test. Br. J. Cancer 37:924930.

Angerer, J., K. Behling, and G. Lehnhart. 1980. Biological workplace tolerance values: BAT value for toluene. Arbeitsmed. Sozialmed. Praeventivmed. 16:161-164.

API (American Petroleum Institute). 1985. Two-Generation Inhalation Reproduction/Fertility Study on a Petroleum Derived Hydrocarbon with Toluene. Study conducted by Internal Research and Development Corporation. API Medical Research Publication No. 32-32854. Washington, DC: American Petroleum Institute.

API (American Petroleum Institute.). 1993. Toluene: The Effect on Pregnancy of the Rat. (Inhalation Exposure). Washington, DC: American Petroleum Institute.

Astrand, I. 1975. Uptake of solvents in the blood and tissues of man: A review. Scand. J. Work Environ. Health 1(4):199-218.

Astrand, I., H. Ehrner-Samuel, A. Kilbom, and P. Ovrum. 1972. Toluene exposure. I. Concentration in alveolar air and blood at rest and during exercise. Work Environ. Health 9:119-130.

ATSDR (Agency for Toxic Substances and Disease Registry). 2000. Toxicological Profile for Toluene (Update). U.S. Department of Health and Human Services. Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA [online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp56.pdf [accessed Apr. 4, 2014].

ATSDR (Agency for Toxic Substances and Disease Registry). 2008. Toxicological Profile for Cresols. U.S. Department of Health and Human Services. Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA [online]. Available: http://www.atsdr.cdc.gov/toxprofiles/tp34.pdf [accessed Apr. 4, 2014].

Baelum, J., I. Andersen, G.R. Lundqvist, L. Mohave, O.F. Pedersen, M. Vaeth, and D.P. Wyon. 1985. Response of solvent-exposed printers and unexposed controls to sixhour toluene exposure. Scand. J. Work Environ. Health 11(4):271-280.

Baelum, J., M. Dossing, S.H. Hansen, G.R. Lundqvist, and N.T. Andersen. 1987. Toluene metabolism during exposure to varying concentrations combined with exercise. Int. Arch. Occup. Environ. Health 59(3):281-294.

Baelum, J., G.R. Lundqvist, L. Molhave, and N.T. Andersen. 1990. Human response to varying concentrations of toluene. Int. Arch. Occup. Environ. Health 62(1):65-72.

Bass, M. 1970. Sudden sniffing death. J. Am. Med. Assoc. 212(2):2075-2079.

Batlle, D.C., S. Sabatini, and N.A. Kurtzman. 1988. On the mechanism of tolueneinduced renal tubular acidosis. Nephron 49(3):210-218.

Bauchinger, M., E. Schmid, J. Dresp, J. Kolin-Gerresheim, R. Hauf, and E. Suhr. 1982. Chromosome change in lymphocytes after occupational exposure to toluene. Mutat. Res. 102(4):439-445.

Benignus, V.A. 1981. Health effects of toluene: A review. Neurotoxicology 2(3):567-588.

Benignus, V.A., K.E. Muller, C.N. Barton, and J.A. Bittikofer. 1981. Toluene levels in blood and brain of rats during and after respiratory exposure. Toxicol. Appl. Pharmacol. 61(3):326-334.

Benignus, V.A., K.E. Muller, J.A. Graham, and C.N. Barton. 1984. Toluene levels in blood and brain of rats as a function of toluene level in inspired air. Environ. Res. 33(1):39-46.

Benignus, V.A., W.K. Boyes, and P.J. Bushnell. 1998. A dosimetric analysis of behavioral effects of acute toluene exposure in rats and humans. Toxicol. Sci. 43(2):186-195.

Benignus, V.A., T. Coleman, C.R. Eklund, and E.M. Kenyon. 2006. A general physiological and toxicokinetic (GPAT) model for simulating complex toluene exposure scenarios in humans. Toxicol. Mech. Methods 16(1):27-36.

Benignus, V.A., W.K. Boyes, E.M. Kenyon, and P.J. Bushnell. 2007. Quantitative comparison of the acute neurotoxicity of toluene in rats and humans. Toxicol. Sci. 100(1):146-155.

Benignus, V.A., P.J. Bushnell, W.K. Boyes, C. Eklund, and E.M. Kenyon. 2009. Neurobehavioral effects of acute exposure to four solvents: Meta-analyses. Toxicol. Sci. 109(2):296-305.

Benignus, V.A., P.J. Bushnell, and W.K. Boyes. 2011. Estimated rate of fatal automobile accidents attributable to acute solvent exposure at low inhaled concentrations. Risk Anal. 31(12):1935-1948.

Benoit, F.M., W.R. Davidson, A.M. Lovett, S. Nacson, and A. Nago. 1985. Breath analysis by API/MS human exposure to volatile organic solvents. Int. Arch. Occup. Environ. Health 55(2):113-120.

Bessems, J., J. Lammers, G. Schaafsma, T. Bouwman, L. Ravensberg, and A. Friedig. 2004. Impact of Peak Exposure and Biological Variability on the Kinetics of Toluene in Man - a PBTK Analysis. Poster Presented at the Society of Toxicology Meeting, March 25, 2004, Baltimore, MD.

Billings, C.E., and L.C. Jonas. 1981. Odor thresholds in air as compared to threshold limit values. Am. Ind. Hyg. J. 42(6):479-480.

Boey, K.W., S.C. Foo, and J. Jeyaratnam. 1997. Effects of occupational exposure to toluene: A neuropsychological study on workers in Singapore. Ann. Acad. Med. Singapore 26(2):184-187.

Bonnet, P., G. Raoult, and D. Gradiski. 1979. Concentration lethales 50 des principaux hydrocarbures aromatiques. Arch. Mal. Prof. Med. Trav. Secur. Soc. 40:805-810 (as cited in ACGIH 2005).

Boor, J.W., and H.I. Hurtig. 1977. Persistent cerebellar ataxia after exposure to toluene. Ann. Neurol. 2(5):440-442.

Bos, R.P., R.M. Brouns, R. Van Doorn, J.L.G. Theuws, and P.T. Henderson. 1981. Nonmutagenicity of toluene, o-, m-, and p-xylene, o-methylbenzyl alcohol and omethylbenzyl sulfate in the Ames assay. Mutat. Res. 88(3):273-279.

Bowen, S.E., and R.L. Balster. 1998. A direct comparison of inhalant effects on locomotor activity and schedule-controlled behavior in mice. Exp. Clin. Psychopharmacol. 6(3):235-247.

Brown, R.P., M.D. Delp, S.L. Lindstedt, L.R. Rhomberg, and R.P. Beliles. 1997. Physiological parameter values for physiologically based pharmacokinetic models. Toxicol. Ind. Health 13(4):407-484.

Bruckner, J.V., and R.G. Peterson. 1981a. Evaluation of toluene and acetone inhalant abuse. I. Pharmacology and pharmacodynamics. Toxicol. Appl. Pharmacol. 61(1):27-38.

Bruckner, J.V., and R.G. Peterson. 1981b. Evaluation of toluene and acetone inhalant abuse. II. Model development and toxicology. Toxicol. Appl. Pharmacol. 61(3):302-312.

Bruckner, J.V., and D.A. Warren. 2001. Toxic effects of solvents and vapors. Pp. 891892 in Casarett & Doull's Toxicology: The Basic Science of Poisons, 6th Ed, C.D. Klaassen, ed. New York: McGraw-Hill.

Bruckner, J.V., D.A. Keys, and J.W. Fisher. 2004. The Acute Exposure Guideline Level (AEGL) program: Applications of physiologically based pharmacokinetic modeling. J. Toxicol. Environ. Health A 67(8-10):621-634.

Brugnone, F. 1985. Uptake of solvents from the lungs. Br. J. Ind. Med. 42(8):569.

Brugnone, F., L. Perbellini, P. Apostoli, M. Locatelli, and P. Mariotto. 1983. Decline of blood and alveolar toluene concentration following two accidental human poisonings. Int. Arch. Occup. Environ. Health 53(2):157-165.

Brugnone, F., E. De Rosa, L. Perbellini, and G.B. Bartolucci. 1986. Toluene concentrations in the blood and alveolar air of workers during the workshift and the morning after. Br. J. Ind. Med. 43(1):56-61.

Bushnell, P.J., H.L. Evans, and E.D. Palmes. 1985. Effects of toluene inhalation on carbon dioxide production and locomotor activity in mice. Fundam. Appl. Toxicol. 5(5):971-977.

Bushnell, P.J., K.L. Kelly, and K.M. Crofton. 1994. Effects of toluene inhalation on detection of auditory signals in rats. Neurotoxicol. Teratol. 16(2):149-160.

Bushnell, P.J., W.M. Oshiro, T.E. Samsam, V.A. Benignus, Q.T. Krantz, and E.M. Kenyon. 2007a. A Dosimetric analysis of the acute behavioral effects of inhaled toluene in rats. Toxicol. Sci. 99(1):181-189.

Bushnell, P.J., J. W.M. Oshiro, T.E. Samsam, and R. Klinger. 2007b. The role of physical activity and feeding schedule on the kinetics of inhaled and oral toluene in rats. J. Toxicol. Environ. Health A 70(21):1806-1814.

Cameron, G.R., J.H. Paterson, G.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. J. Pathol. Bacteriol. 46(1):95-107.

Carder, J.R., and R.S. Fuerst. 1997. Myocardial infarction after toluene inhalation. Pediatr. Emerg. Care 13(2):117-119.

Carlsson, A. 1982. Exposure to toluene: Uptake, distribution and elimination in man. Scand. J. Work Environ. Health 8(1):43-55.

Carlsson, A., and T. Lindqvist. 1977. Exposure of animals and man to toluene. Scand. J. Work Environ. Health 3(3):135-143.

Carpenter, A.V., W.D. Flanders , E.L. Frome, W.G. Tankersley, and S.A. Fry. 1988. Chemical exposures and central nervous system cancers: A case-control study among workers at two nuclear facilities. Am. J. Ind. Med. 13(3):351-362.

Carpenter, C.P., C.B. Schaffer, C.S. Weil, and H.F. Smyth. 1944. Studies on the inhalation of 1,3-butadiene with a comparison of its narcotic effect with benzol, toluol, and

styrene and a note on the elimination of styrene by the human. J. Ind. Hyg. Toxicol. 26(3):69-78.

Carpenter, C.P., D.L. Geary, R.C. Myers, D.J. Nachreiner, L.J. Sullivan, and J.M. King. 1976. Petroleum hydrocarbon toxicity studies. XIII. Animal and human response to vapors of toluene concentrate. Toxicol. Appl. Pharmacol. 36(3):473-490.

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.

Chemical Week. 2000. Toluene. Chemical Week, P. 33. March 1, 2000.

Cherry, N., J.D. Johnston, H. Venables, H.A. Waldron, L. Buck, and C.J. MacKay. 1983. The effects of toluene and alcohol on psychomotor performance. Ergonomics 26(11):1081-1087.

CIR (Cosmetic Ingredient Review). 1987. Final report on the safety assessment of toluene. Int. J. Toxicol. 6(1):77-120.

Cohr, K.J., and J. Stockholm. 1979. Toluene: A toxicological review. Scand. J. Work Environ. Health 5(2):71-90.

Cometto-Muniz, J.E., and W.S. Cain. 1995. Relative sensitivity of the ocular trigeminal, nasal trigeminal and olfactory systems to airborne chemicals. Chem. Senses 20(2):191-198.

Courtney, K., J. Andrews, J. Springer, M. Memnache, T. Williams, L. Dalley, and J. Graham. 1986. A perinatal study of toluene in CD-1 mice. Fundam. Appl. Toxicol. 6(1):145-154.

Cunningham, S.R., G.W. Dalzell, P. McGirr, and M.M. Khan. 1987. Myocardial infarction and primary ventricular fibrillation after glue sniffing. Br. Med. J. 294(6574):739-740.

Dalgaard, M., A. Hossaini, K.S. Hougaard, U. Hass, and O. Ladefoged. 2001. Developmental toxicity of toluene in male rats: Effects on semen quality, testis morphology, and apoptotic neurodegeneration. Arch. Toxicol. 75(2):103-109.

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 Ceaurriz Jr., J., J.P. Desiles, P. Bonnet, B. Marignac, J. Muller, and J.P. Guenier. 1983. Concentration-dependent behavioral changes in mice following short-term inhalation exposure to various industrial solvents. Toxicol. Appl. Pharmacol. 67(3):383-389.

DeJongh, J., and B. J. Blaauboer. 1996. Simulation of toluene kinetics in the rat by a physiologically based pharmacokinetic model with application of biotransformation parameters derived independently in vitro and in vivo. Fundam. Appl. Toxicol. 32(2):260-268.

Dennison, J.E., C.M. Troxel, and R. Benson. 2010. PBPK modeling white paper: Addressing the use of PBPK models to support derivation of acute exposure guideline levels. Pp. 381-446 in Acute Exposure Guideline Levels for Selected Airborne Chemicals, Vol. 9. Washington, DC: The National Academies Press.

Deschamps, D., C. Geraud, and S. Dally. 2001. Cognitive functions in workers exposed to toluene: Evaluation at least 48 hours after removal from exposure. Int. Arch. Occup. Environ. Health 74(4):285-288.

DFG (Deutsche Forschungsgemeinschaft). 1999. List of MAK and BAT Values, 1999. Maximum Concentarations and Biological Tolerance Value at the Workplace Report No. 35. Weinheim, Federal Republic of Germany: Wiley-VCH.

Dick, R.B., J.V. Setzer, R. Wait, M.B. Hayden, B.J. Taylor, B. Tolos, and V. PutzAnderson. 1984. Effects of acute exposure of toluene and methyl ethyl ketone on psychomotor performance. Int. Arch. Occup. Environ. Health 54(2):91-109.

Dobrokhotov, V.B. 1972. Mutagenic effect of benzene and toluene under experimental conditions [in Russian]. Gig. Sanit. 37(10):36-39.

Dobrokhotov, V.B., and M.I. Enikeev. 1975. The mutagenic effect of benzene, toluene, and a mixture of these hydrocarbons in a chronic experiment [in Russian]. Gig. Sanit. 1:32-34.

Donald, J.M., K. Hooper, and C. Hopenhayn-Rich. 1991. Reproductive and developmental toxicity of toluene: A review. Environ. Health Perspect. 94:237-244.

Dossing, M, J. Baelum, S.H. Hansen, and G.R. Lundqvist. 1984. Effect of ethanol, crimetidine and propranolol on toluene metabolism in man. Int. Arch. Occup. Environ. Health 54(4):309-315.

DuPont (E.I. du Pont de Nemours and Company). 1966. Acute Inhalation Toxicity: Toluene. Haskell Laboratory Report 4427. EPA Document No. 878220472. Microfiche No. OTS0215044.

Echeverria, D., L. Fine, G. Langolf, A. Schork, and C. Sampaio. 1989. Acute neurobehavioral effects of toluene. Br. J. Ind. Med. 46(7):483-495.

Echeverria, D., L. Fine, G. Langolf, T. Schork, and C. Sampaio. 1991. Acute behavioral comparisons of toluene and ethanol in human subjects. Br. J. Ind. Med. 48(11):750-761.

Eller, N., B. Netterstrom, and P. Laursen. 1999. Risk of chronic effects on the central nervous system at low toluene exposure. Occup. Med. 49(6):389-395.

EPA (U.S. Environmental Protection Agency). 1990. Drinking Water Criteria Document for Toluene. Environmental Criteria and Assessment, Office of Health and Environmental Assessment. U.S. Environmental Protection Agency, Cincinnati, OH. July 1990.

EPA (U.S. Environmental Protection Agency). 2007. Toluene. Integrated Risk Information System. U.S. Environmental Protection Agency [online]. Available: http://www.epa.gov/iris/subst/0118.htm [accessed Apr. 5, 2014].

Evans, E.L., and A.D. Mitchell. 1980. An Evaluation of the Effect of Toluene on Sister Chromatid Exchange Frequencies in Cultured Chinese Hamster Ovary Cells. SRI International, Menlo Park, CA. EPA Contract No. 68-02-2947.

Fischman, C.M., and J.R. Oster. 1979. Toxic effect of toluene: A new cause of high anion gap metabolic acidosis. J. Am. Med. Assoc. 241(16):1713-1715.

Fiserova-Bergerova, V., and M.L. Diaz. 1986. Determination and prediction of tissue-gas partition coefficients. Int. Arch. Occup. Environ. Health 58(1):75-87.

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.

Fluck, E.R., L.A. Poirier, and H.W. Ruelius. 1976. Evaluation of a DNA polymeraedeficient mutant of E. coli for the rapid detection of carcinogens. Chem. Biol. Interact. 15(3):219-231.

Foo, S.C., W.O. Phoon, and N.Y. Khoo. 1988. Toluene in blood after exposure to toluene. Am. Ind. Hyg. Assoc. J. 49(5):255-258.

Foo, S.C., J. Jeyarathnam, and D. Koh. 1990. Chronic neurobehavioral effects of toluene. Br. J. Ind. Med. 47(7):480-484.

Forni, A., E. Pacifico, and A. Limonta. 1971. Chromosome studies in workers exposed to benzene or toluene or both. Arch. Environ. Health 22(3):373-378.

Gad-El-Karim, M.M., B.L. Harper, and M.S. Legator. 1984. Modifications in the myeloclastogenic effect of benzene in mice with toluene, phenobarbital, 3methylcholanthrene, Aroclor 1254 and SKF-252A. Mutat. Res. 135(3):225-243.

Gamberale, F., and M. Hultengren. 1972. Toluene exposure. II. Psychophysiological functions. Work Environ. Health 9(3):131-139.

Garcia, H.D. 2008. Toluene. Pp. 329-347 in Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants, Vol. 5. Washington, DC: The National Academies 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.

Geller, I., R. Hartmann, S. Randle, and E.M. Gause. 1979. Effects of acetone and toluene vapors on multiple schedule performance of rats. Pharmacol. Biochem. Behav. 11(4):395-399.

Gerasimov, M.R., R.A. Ferrieri, W.K. Schiffer, J. Logan, S.J. Gatley, A.N. Gifford, D.A. Alexoff, D.A. Marsteller, C. Shea, V. Garza, P. Carter, P. King, C.R. Ashby, Jr., S. Vitkun, and S.L. Dewey. 2002. Study of brain uptake and biodistribution of [^{11}C]toluene in non-human primates and mice. Life Sci. 70(23):2811-2828.

Gericke, C., B. Henke, G. Beckmann, M.M. Baltes, K.P. Kuhl, and D. Neubert. 2001. Multicenter field trial on possible health effects of toluene. III. Evaluation of effects after long-term exposure. Toxicology 168(2):185-209.

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.

Gibson, J.E., and J.F. Hardisty. 1983. Chronic toxicity and oncogenicity bioassay of inhaled toluene in Fischer-344 rats. Fundam. Appl. Toxicol. 3(4):315-319.

Glowa, J. 1981. Some effects of sub-acute exposure to toluene on schedule-controlled behavior. Neurobehav. Toxicol. Teratol. 3(4):463-465.

Glowa, J.R., J. DeWeese, M.E. Natole, J.J. Holland, and P.B. Dews. 1986. Behavioral toxicology of volatile organic solvents. I. Methods: acute effects of toluene. J. Environ. Pathol. Toxicol. Oncol. 6(5-6):153-158.

Gospe, S.M., and M.A.S. Al-Bayati. 1994. Comparison of oral and inhalation exposure to toluene. J. Am. Coll. Toxicol. 13(1):21-32.

Gospe, S.M., and M.J. Calaban. 1988. Central nervous system distribution of inhaled toluene. Fundam. Appl. Toxicol. 11(3):540-545.

Greenberg, L., M.R. Mayers, H. Heiman, and S. Moskowitz. 1942. The effects of exposure to toluene in industry. J. Am. Med. Assoc. 118(8):573-578.

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

Gupta, R.K., J. van der Meulen, and K.V. Johny. 1991. Oliguric acute renal failure due to glue-sniffing. Scand. J Urol. Nephrol. 25(3):247-250.

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

Hammer, K.D. 2002. Metabolite ratio of toluene-exposed rotogravure printing plant workers reflects individual mutagenic risk by sister chromatid exchanges. Mutat. Res. 519(1-2):171-177.

Harabuchi, I, R. Kishi, T. Ikeda, H. Kiyosawa, and H. Miyake. 1993. Circadian variations of acute toxicity and blood and brain concentrations of inhaled toluene in rats. Br. J. Ind Med. 50(3):280-286.

Hasegawa, K., S. Shiojima, A. Koizumi, and M. Ikeda. 1983. Hippuric acid and o-cresol in the urine of workers exposed to toluene. Int. Arch. Occup. Environ. Health. 52(3):197-208.

Haworth, S., T. Lawlor, K. Mortelmans, W. Speck, and E. Zeiger. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. 5(suppl. 1):1-142.

Hellman, T.M., and F.H. Small. 1974. Characterization of the odor properties of 101 petrochemicals using sensory methods. J. Air Pollut. Control Assoc. 24(10):979-982.

Henderson, R. 2001. Aromatic hydrocarbons - benzene and other alkylbenzenes. Pp. 231301 in Patty's Toxicology, Vol. 4, 5th Ed. New York: John Wiley & Sons.

Hinman, D. 1987. Biphasic dose-response relationship for effects of toluene inhalation on locomotor activity. Pharmacol. Biochem. Behav. 26(1):65-69.

Hjelm, E.W., P.H. Naslund, and M. Wallen. 1988. Influence of cigarette smoking on the toxicokinetics of toluene in humans. J. Toxicol. Environ. Health 25(2):155-163.

Hobara, T. M. Okuda, M. Gotoh, K. Oki, H. Segawa, and I. Kunitsugu. 2000. Estimation of the lethal toluene concentration from the accidental death of painting workers. Ind. Health 38(2):228-231.

Horvath, M., E. Frantik, and P. Krekule. 1981. Diazepam impairs alertness and potentiates the similar effect of toluene. Homeostasis 23:177-179.

Hougaard, K.S., A.M. Hansen, U. Hass, and S.P. Lund. 2003. Toluene depresses plasma corticosterone in pregnant rats. Pharmacol. Toxicol. 92(3):148-152.

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

IARC (International Agency for Research on Cancer). 1989. Toluene. Pp. 79-123 in Some Organic Solvents, Resin Monomers, and Related Compounds, Pigments, and Occupational Exposures in Paint Manufacture and Painting. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 47. Lyon, France: IARC Press [online]. Available: http://monographs.iarc.fr/ENG/Monographs/vol47/mono47.pdf [accessed Apr. 4, 2014].

IARC (International Agency for Research on Cancer). 1999. Toluene. Pp. 829-864 in Reevaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Vol. 71(Part 2). Lyon France: IARC Press [online]. Available: http://monographs. iarc.fr/ENG/Monographs/vol71/mono71.pdf [accessed Apr. 4, 2014].

Ikeda, M. 1974. Reciprocal metabolic inhibition of toluene and trichloroethylene in vivo and in vitro. Int. Arch. Arbeitsmed. 33(2):125-133.

Ikeda, N., H. Takahashi, K. Umetsu, and T. Suzuki. 1990. The course of respiration and circulation in “toluene-sniffing”. Forensic Sci. Int. 44(2-3):151-158.

Iregren, A. 1982. Effects on psychological test performance of workers exposed to a single solvent (toluene) - A comparison with effects of exposure to a mixture of organic solvents. Neurobehav. Toxicol. Terat. 4(6):695-701.

Iregren, A., T. Akerstedt, B.A. Olsen, and F. Gamberale. 1986. Experimental exposure to toluene in combination with ethanol intake. Scand. J. Work Environ. Health 12(2):128-136.

Jenkins, L.J., R.A. Jones, and J. Siegel. 1970. Long-term inhalation screening studies of benzene, toluene, o-xylene, and cumene on experimental animals. Toxicol. Appl. Pharmacol. 16(3):818-823.

Johnson, A.C., and B. Canlon. 1994. Progressive hair cell loss induced by toluene exposure. Hear. Res. 75(1-2):201-208.

Jone, C.M., A.H. Wu. 1988. An unusual case of toluene-induced metabolic acidosis. Clin. Chem. 34(12):2596-2599.

Jonsson, F., F. Bois, and G. Johanson. 2001. Physiologically based pharmacokinetic modeling of inhalation exposure of humans to dichloromethane during moderate to heavy exercise. Toxicol. Sci. 59(2):209-218.

Juntunen, J., E. Matikainen, M. Antti-Poika, H. Suoranta, and M. Valle. 1985. Nervous system effects of long-term occupational exposure to toluene. Acta Neurol. Scand. 72(5):512-517.

Kamijima, M., Y. Nakazawa, M. Yamakawa, E. Shibata, N. Hisanaga, Y. Ono, M. Toida, and Y. Takeuchi. 1994. Metabolic acidosis and renal tubular injury due to pure toluene inhalation. Arch. Environ. Health 49(5):410-413.

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

Kenyon, E.M., V. Benignus, C. Eklund, J.W. Highfill, W.M. Oshiro, T.E. Samsam, and P.J. Bushnell. 2008. Modeling the toxicokinetics of inhaled toluene in rats: Influence of physical activity and feeding status. J. Toxicol. Environ. Health A 71(4):249-265.

Kezic, S., A.C. Monster, J. Kruse, and M.M. Ververk. 2000. Skin absorption of some vaporous solvents in volunteers. Int. Arch. Occup. Environ. Health 73(6):415-422.

King, M.D., R.E. Day, J.S. Oliver, M. Lush, and J.M. Watson. 1981. Solvent encephalopathy. Br. Med. J. 283(6292):663-665.

Kirkhart, B. 1980. Micronucleus Test on Toluene. SRI International, Menlo Park, CA. EPA Contract No. 68-02-2947.

Kishi, R., I. Harabuchi, T. Ikeda, H. Yokota, and H. Miyake. 1988. Neurobehavioral effects and pharmacokinetics of toluene in rats and their relevance to man. Br. J. Ind. Med. 45(6):396-408.

Klimisch, H.J., J. Hellwig, and A. Hoffman. 1992. Studies on the prenatal toxicity of toluene in rabbits following inhalation exposure and proposal of a pregnancy guidance value. Arch. Toxicol. 66(6):373-381.

Kobayashi, K. 1985. Experimental studies on acute toluene poisoning. Shikoku Acta Med. 41:82-94.

Kobayashi, H., T. Hobara, and T. Sakai. 1989. Effects of inhalation of several organic solvents on left ventricular dp/dt [in Japanese]. Sangyo Igaku 31(3):136-141.

Kojima, T., and H. Kobayashi. 1973. Toxicological study on toluene poisoning by inhalation - correlation of toluene concentration for exposure with mortality and toluene tissue level. Nippon Hoigaku Zasshi 27:282-296.

Korsak, Z., J. Sokal, and R. Swiercz. 1991. The toxic effects of combined exposure to toluene and m-xylene in animals. II. Blood toluene and m-xylene during single and combined exposure in rats. Pol. J. Occup. Med. Environ. Health 4(4):377-382.

Krewski, D., K. Bakshi, R. Garrett, E. Falke, G. Rusch, and D. Gaylor. 2004. Development of acute exposure guideline levels for airborne exposures to hazardous substances. Regul. Toxicol. Pharmacol. 39(2):184-201.

Kroeger, R.M., R.J. Moore, T.H. Lehman, J.D. Giesy, and C.E. Skeeters. 1980. Recurrent urinary calculi associated with toluene sniffing. J. Urol. 123(1):89-91.

Lammers, J.H., W.J. Meuling, H. Muijser, A.P. Freid, and J.G. Bessems. 2005a. Neurobehavioral evaluation and kinetics of inhalation of constant or fluctuating toluene concentrations in human volunteers. Environ. Toxicol. Pharmacol. 20(3):431-442.

Lammers, J.H., J. van Asperen, D. de Groot, and W.R. Rijcken. 2005b. Behavioural effects and kinetics in brain in response to inhalation of constant or fluctuating toluene concentration in the rat. Environ. Toxicol. Pharmacol. 19(3):625-634.

LBI (Litton Bionetics, Inc). 1978. Mutagenicity Evaluation of Toluene. Final Report. LBI Project No. 20847. Washington, DC: American Petroleum Institute.

LBI (Litton Bionetics, Inc). 1981. Mutagenicity Evaluation of Toluene-Mouse Dominant Lethal Assay. Final Report. LBI Project No. 20847. Washington, DC: American Petroleum Institute.

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

Lee, B.K., S.H. Lee, K.M. Lee, K.S. Cho, K.D. Ahn, S.B. Kim, H. Ukai, H. Nakatsuka, T. Watanabe, and M. Ikeda. 1988. Dose-dependent increase in subjective symptom prevalence among toluene-exposed workers. Ind. Health 26(1):11-23.

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.

Liira, J., E. Elovaara, H. Raunio, V. Riihimaki, and K. Engstrom. 1991. Metabolic interaction and disposition of methyl ethyl ketone and m-xylene in rats at single and repeated inhalation exposures. Xenobiotica 21(1):53-63.

Litt, I.F., M.L. Cohen, S.K. Schonberg, and I. Spigland. 1972. Liver disease in the drugusing adolescent. J. Pediatr. 81(2):238-242.

Lof, A., M. Wallen, and E.W. Hjelm. 1990. Influence of paracetamol and acetylsalicylic acid on the toxicokinetics of toluene. Pharmacol. Toxicol. 66(2):138-141.

Lof, A., E.W. Hjelm, A. Colmsjo, B.O. Lundmark, A. Norström, and A. Sato. 1993. Toxicokinetics of toluene and urinary excretion of hippuric acid after human exposure to ^{2}H-toluene. Br. J. Ind. Med. 50(1):55-59.

Longley, E.O., A.T. Jones, R. Welch, R., and O. Lomaev. 1967. Two acute toluene episodes in merchant ships. Arch. Environ. Health 14(3):481-487.

Low, L.K., J.R. Meeks, and C.R. Mackerer. 1988. Health effects of the alkylbenzenes. I. Toluene. Toxicol. Ind. Health 4(1):49-75.

Luderer, U., M.S. Morgan, C.A. Brodkin, D.A. Kalman, and E.M. Faustman. 1999. Reproductive endocrine effects of acute exposure to toluene in men and women. Occup. Environ. Med. 56(10):657-666.

Lyapkalo, A.A. 1973. Genetic activity of benzene and toluene [in Russian]. Gig. Tr. Prof. Zabol. 17(3):24-28.

Magos, G.A., M. Lorenzana-Jimenez, and H. Vidrio. 1990. Toluene and benzene inhalation influences on ventricular arrhythmias in the rat. Neurotoxicol. Teratol. 12(2):119-124.

Maki-Paakkanen, J. K. Husgafvel-Pursiainen, P.L. Kalliomaki, J. Tuominen, and M. Sorsa. 1980. Toluene-exposed workers and chromosome aberrations. J. Toxicol. Environ. Health 6(4):775-781.

Marjot, R., and A.A. McLeod. 1989. Chronic non-neurological toxicity from volatile substance abuse. Hum. Toxicol. 8(4):301-306.

Massengale, O.N., H.H. Glaser, R.E. LeLievre, J.B. Dobbs, and M.E. Klock. 1963. Physical and psychologic factors in glue sniffing. N. Engl. J. Med. 269:1340-1344.

McCarroll, N.E., B.H. Keech, and C.E. Piper. 1981a. A microsuspension adaptation of the Bacillus subtilis "rec" assay. Environ. Mutagen. 3(6):607-616.

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

McGregor, D.B., A. Brown, P. Cattanach, I. Edwards, D. McBride, C. Riach, and W.J. Caspary. 1988. Responses of the L5178Ytk^{+}/tk^{-} mouse lymphoma cell forward mutation assay. III. 72 coded chemicals. Environ. Mole. Mutagen. 12(1):85-154.

Mergler, D., and B. Beauvais. 1992. Olfactory threshold shift following controlled 7-hour exposure to toluene and/or xylene. Neurotoxicology 13(1):211-215.

Meulenbelt, J., G. de Groot, and T.J. Savelkoul. 1990. Two cases of acute toluene intoxication. Br. J. Ind. Med. 47(6):417-420.

Miyagawa, M., T. Honma, M. Sato, and H. Hasegawa. 1984. Effects of a single exposure to toluene on operant behavior and brain toluene levels in rats. Ind. Health 22(2):127-131.

Miyagawa, M., T. Honma, M. Sato, and H. Hasegawa. 1986. Behavioral change after single exposure to toluene, and brain toluene levels in rats. Ind. Health 24(3):157-161.

Morata, T.C., A.C. Fiorini, F.M. Fischer, S. Colacioppo, K.M. Wallingford, E.F. Krieg, D.E. Dunn, L. Gozzoli, M.A. Padrão, and C.L. Cesar. 1997. Toluene-induced hearing loss among rotogravure printing workers. Scand. J Work Environ. Health 23(4):289-298.

Mortelmans, K.E., and E.S. Riccio. 1980. In vitro Microbiological Genotoxicity Assays of Toluene. SRI International, Menlo Park, CA. EPA Contract No. 68-02-2947.

Moser, V.C., and R.L. Balster. 1981. The effects of acute and repeated toluene exposure on operant behavior in mice. Neurobehav. Toxicol. Teratol. 3(4):471-475.

Moser, V.C., and R.L. Balster. 1985. Acute motor and lethal effects of inhaled toluene, 1,1,1-trichloroethane, halothane, and ethanol in mice: Effects of exposure duration. Toxicol. Appl. Pharmacol. 77(2):285-291.

Moss, A.H., P.A. Gabow, W.D. Kaehny, W.D. Goodman, L.L. Haut, and M.R. Hassler. 1980. Fanconi's syndrome and distal renal tubular acidosis after glue sniffing. Ann. Intern. Med. 92(1):69-70.

MSZW (Ministerie van Sociale Zaken en Werkgelegenheid). 2004. Nationale MAC-lijst 2004: Tolueen. Den Haag: SDU Uitgevers [online]. Available: http://www.lasrook.net/lasrookNL/maclijst2004.htm [accessed Apt 5, 2014].

Mullin, L.S., and N.D. Krivanek. 1982. Comparison of unconditioned reflex and conditioned avoidance tests in rats exposure by inhalation to carbon monoxide, 1,1,1trichloroethane, toluene or ethanol. Neurotoxicity 3(1):126-137.

Murata, K., S. Araki, K. Yokoyama, T. Tanigawa, K. Yamashita, F. Okajima, T. Sakai, C. Matsungag, and K. Suwa. 1993. Cardiac autonomic dysfunction in rotogravure printers exposed to toluene in relation to peripheral nerve conduction. Ind. Health 31(3):79-90.

Muttray, A., U. Spelmeyer, G. Hommel, F. Oesch, D. Jung, D.M. Rose, O. MayerPopken, B. Rossbach, and S. Letzel. 2005. Acute exposure to 50 ppm toluene does not increase sleepiness. Environ. Toxicol. Pharmacol. 19(3):665-669.

Nadeau, V., G. Truchon, M. Brochu, and R. Tardif. 2006. Effect of physical exertion on the biological monitoring of exposure of various solvents following exposure by inhalation in human volunteers: I. Toluene. J. Occup. Environ. Hyg. 3(9):481-489.

Nakajima, T., R.S. Wang, Y. Katakura, R. Kishi, E. Elovaara, S.S. Park, H.V. Gelboin, and H. Vainio. 1992. Sex-, age-, and pregnancy-induced changes in the metabolism of toluene and trichloroethylene in rat liver in relation to the regulation of cytochrome P45011E1 and P45011C11 content. J. Pharmacol. Exp. Ther. 261(3):869-874.

Nakajima, T., R.S. Wang, E. Elovaara, F.J. Gonzalez, H.V. Gelboin, H. Raunio, O. Pelkonen, H. Vainio, and T. Aoyama. 1997. Toluene metabolism by cDNAexpressed human hepatic cytochrome P450. Biochem. Pharmacol. 53(3):271-277.

Nestmann, E.R., E.G.H. Lee, T.I. Matula, G.R. Douglas, and J.C. Mueller. 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian-microsome assay. Mutat. Res. 79(3):203-212.

Neubert, D., C. Gericke, B. Hanke, G. Beckmann, M.M. Baltes, K.P. Kuhl, G. Bochert, and J. Hartmann. 2001a. Multicenter field trial on possible health effects of toluene. II. Cross-sectional evaluation of acute low-level exposure. Toxicology 168(2):159-183.

Neubert, D., G. Bochert, C. Gericke, B. Hanke, and G. Beckmann. 2001b. Multicenter field trial on possible health effects of toluene. I. Toluene body burdens in workers of the rotogravure industry. Toxicology 168(2):139-157.

Ng, T., S. Foo, and T. Yoong. 1992. Menstrual function in workers exposed to toluene. Br. J. Ind. Med. 49(11):799-803.

Nielsen, G.D., and Y. Alarie. 1982. Sensory irritation, pulmonary irritation and respiratory stimulation by airborne benzene and alkylbenzenes: Prediction of safe industrial exposure levels and correlation with their thermodyamic properties. Toxicol. Appl. Pharmacol. 65(3):457-477.

Nielsen, H.K., L. Krusell, J. Baelum, G. Lundqvist, O. Omland, M. Vaeth, M., S.E. Husted, C.E. Mogensen, and E. Geday. 1985. Renal effects of acute exposure to toluene: A controlled clinical trial. Acta Med. Scand. 218(3):317-321.

NIOSH (National Institute for Occupational Safety and Health). 1973. Criteria for a Recommended Standard... Occupational Exposure to Toluene. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/docs/ 1970/73-11023.html [accessed Apr. 4, 2014].

NIOSH (National Institute for Occupational Safety and Health). 1985. FACE Report: Confined Space Incident Kills Two Workers Company Employee and Rescuing Fireman. Report No. FACE-85-5. U.S. Department of Health and Hyman Services, Morgantown, WV [online]. Available: http://www.cdc.gov/niosh/fire/reports/face 8505.html [accessed Apr. 4, 2014].

NIOSH (National Institute for Occupational Safety and Health). 1994. Documentation for Immediately Dangerous To Life or Health Concentrations (IDLHs): Toluene. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/idlh/108883.html [accessed Apr. 7, 2014].

NIOSH (National Institute for Occupational Safety and Health). 2011. NIOSH Pocket Guide to Chemical Hazards: Toluene. National Institute for Occupational Safety and Health [online]. Available: http://www.cdc.gov/niosh/npg/npgd0619.html [accessed Apr. 4, 2014].

Nomiyama, K., and H. Nomiyama. 1978. Three fatal cases of thinner-sniffing and experimental exposure to toluene in humans and animals. Int. Arch. Occup. Environ. Health 41(1):55-64.

NRC (National Research Council). 1981. The Alkyl Benzenes. 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). 2008. Toluene. Pp. 230-275 in Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 2. Washington, DC: The National Academies Press.

NTP (National Toxicology Program). 1990. Toxicology and Carcinogenesis Studies of Toluene. (CAS No. 108-88-3) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies). NTP-TR-371. NIH 90-2826. U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, National Toxicology Program, Research Triangle Park, NC [online]. Available: http://ntp.niehs.nih.gov/ntp/ht docs/lt_rpts/tr371.pdf [accessed Apr. 4, 2014].

O'Brien, E.T., W.B. Yeoman, and J.A.E. Hobby. 1971. Hepatorenal damage from toluene in a "glue sniffer." Br. Med. J. 2(5752):29-30.

Ogata, M. 1984. Estimation of solvent concentrations in ambient air from urinary metaboliste levels of workers expsed to solvents. Ind. Health 22(4):319-324.

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

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.

O'Neil, M.J., A. Smith, and P.E. Heckelman, eds. 2006. Toluene. P.1638 inThe Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 14th ed. Whitehouse Station, NJ: Merck.

Ono, A., K. Sekita, K. Ohno, A. Hirose, Y. Ogawa, M. Saito, K. Naito, T. Kaneko, T. Furuya, K. Matsumoto, S. Tanaka, and Y. Kurokawa. 1995. Reproductive and developmental toxicity studies of toluene. I. Teratogenicity study of inhalation exposure in pregnant rats. J. Toxicol. Sci. 20(2):109-134.

Ono, A., K. Sekita, Y. Ogawa, A. Hirose, S. Suzuki, M. Saito, K. Naito, T. Kaneko, T. Furuya, K. Kawashima, K. Yasuhara, K. Matsumoto, S. Tanaka, T. Inoue, and Y. Kurokawa. 1996. Reproductive and developmental toxicity studies of toluene. II.

Effects of inhalation exposure on fertility in rats. J. Environ. Path. Toxicol. Oncol. 15(1):9-20.

Oshiro, W.M., and P.J. Bushnell. 2004. Acute and repeated inhalation of toluene by rats performing a signal detection task leads to behavioral tolerance on some performance measures. The Toxicologist 98:296. (Poster presented at the Society of Toxicology, March 22, 2004, Baltimore, MD).

Oshiro, W.M., Q.T. Krantz, and P.J. Bushnell. 2007. Repeated inhalation of toluene by rats performing a signal detection task leads to behavioral tolerance on some performance measures. Neurotoxicol. Teratol. 29(2):247-254.

Ovrum, O., M. Hultengren, and T. Lindqvist. 1978. Exposure to toluene in a photogravure printing plant. Concentration in ambient air and uptake in the body. Scand. J. Work Environ. Health 4(3):237-245.

Ozokwelu, E.D. 1997. Toluene. Pp. 350-389 in Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 24, 4th Ed. New York: John Wiley & Sons.

Parmeggiani, L., and C. Sassi. 1954. Occupational hazards from toluene: Atmospheric investigation and clinic findings in chronic poisoning [in Italian]. Med Lav. 45(11):574-583.

Patel, R., and J. Benjamin. 1986. Renal disease associated with toluene inhalation. J. Toxicol. Clin. Toxicol. 24(3):213-223.

Paterson, D.C., and R. Sarvesvaran. 1983. Plastic bag death: A toluene fatality. Med. Sci. Law 23(1):64-66.

Pelekis, M., L.A. Gephart, and S.E. Lerman. 2001. Physiological-model-based derivation of the adult and child pharmacokinetic intraspecies uncertainty factors for volatile organic compounds. Regul. Toxicol. Pharmacol. 33(1):12-20.

Pierce, C.H., R.L. Dills, M.S. Morgan, G.L. Nothstein, D.D. Shen, and D.A. Kalman. 1996a. Interindividual differences in ^{2}H-toluene toxicokinetics assessed by a semiempirical physiologically based model. Toxicol. Appl. Pharmacol. 139(1):49-61.

Pierce, C.H., R.L. Dills, M.S. Morgan, P. Vicini, and D.A. Kalman. 1998. Biological monitoring of controlled toluene exposure. Int. Arch. Occup. Environ. Health 71(7):433-444.

Pierce, C.H., T.A. Lewandowski, R.L. Dills, M.S. Morgan, M.A. Wessels, D.D. Shen, and D.A. Kalman. 1999. A comparison of $^{1}H_{8}$ and $^{2}H_{8}$-toluene toxicokinetics in men. Xenobiotica 29(1):93-108.

Pierce, C.H., Y. Chen, R.L. Dills, D.A. Kalman, and M.S. Morgan. 2002. Toluene metabolites as biological indicators of exposure. Toxicol. Lett. 129(1-2):65-76.

Poon, R., I. Chu, S. Bjarnason, M. Potvin, R. Vincent, R.B. Miller, and V.E. Valli. 1994. Inhalation toxicity study of methanol, toluene, and methanol/toluene mixtures in rats: Effects of 28-day exposure. Toxicol. Indust. Health 10(3):231-245.

Press, E., and A.K. Done. 1967. Solvent sniffing: Physiologic effects and community control measures for intoxication from the intentional inhalation of organic solvents. I. Pediatrics 39(3):451-461.

Pryor, G.T., R.A. Howd, R. Malik, R., R.A. Jensen, and C.S. Rebert. 1978. Biomedical Studies on the Effects of Abused Inhalant Mixtures. Annual Progress Report prepared by SRI International (Contract No. 271-77-3402) for the National Institute on Drug Abuse, Rockville, MD (as cited in ACGIH 2005).

Pryor, G.T., J. Dickinson, E. Feeney, and C.S. Rebert. 1984. Hearing loss in rats first exposed to toluene as weanlings or as young adults. Neurobehav. Toxicol. Teratol. 6(2):111-119.

Purcell, K.J., G.H. Cason, M.L. Gargas, M.E. Andersen, and C.C. Travis. 1990. In vivo metabolic interactions of benzene and toluene. Toxicol. Lett. 52(2):141-152.

Rahill, A.A., B. Weiss, P.E. Morrow, M.W. Frampton, C. Cox, R. Gibb, R. Gelein, D. Speers, and M.J. Utell. 1996. Human performance during exposure to toluene. Aviat. Space Environ. Med. 67(7):640-647.

Reddy, M., R.S.H. Yang, H.J. Clewell, III, and M.E. Andersen. 2005. Physiologically Based Pharmacokinetics: Science and Applications. John Wiley & Sons. 420 pp.

Rees, D.C., R.W. Wood, J.P. McCormick, and C. Cox. 1985. Toxicokinetics of toluene in the rat. Scand. J. Work Environ. Health 11(4):301-306.

Reisin, E., A. Teicher, R. Jaffe, and H.E. Eliahou. 1975. Myoglobinuria and renal failure in toluene poisoning. Br. J. Ind. Med. 32(2):163-164.

Richer, C.L., S. Chakrabarti, M. Senecal-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.

Ron, M. 1986. Volatile substance abuse: A review of possible long-term neurological, intellectual and psychiatric sequelae. Br. J. Psychiatry 148:235-246.

Russ, G., A.R. Clarkson, A.J. Woodroffe, A.E. Seymour, and I.K. Cheng. 1981. Renal failure from "glue sniffing". Med. J. Aust. 2(3):121-122.

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

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

Sato, A., and T. Nakajima. 1979b. Dose-dependent metabolic interaction between benzene and toluene in vivo and in vitro. Toxicol. Appl. Pharmacol. 48(2):249-256.

Schaper, M., P. Demes, M. Zupanic, M. Blaszkewicz, and A. Seeber. 2003. Occupational toluene exposure and auditory function: Results from a follow-up study. Ann. Occup. Hyg. 47(6):493-502.

Seeber, A., P. Demes, E. Kiesswetter, M. Schaper, C. van Thriel, and M. Zupanic. 2005. Changes of neurobehavioral and sensory functions due to toluene exposure below 50 ppm? Environ. Toxicol. Pharmacol. 19(3):635-643.

Shell Oil Company. 1982. Test Standardization Inhalation Toxicity Testing of 8 Chemicals According to the OECD Inhalation Hazard Test with Cover Letter. EPA Document No. 878212113, Microfiche No. OTS0205969.

Sherwood, R.J. 1976. Ostwald solubility coefficients of some industrially important substances. Br. J. Ind. Med. 33(2):106-107.

Shigeta, S., H. Aikawa, T. Misawa, and A. Kondo. 1978. Effect of single exposure to toluene on Sidman avoidance response in rats. J. Toxicol. Sci. 3(4):305-312.

Shigeta, S., H. Aikawa, and T. Misawa. 1981. Effects of toluene exposure during pregnancy on mice fetuses. J. Toxicol. Sci. 6:254-255.

Simmons, J.E., W.K. Boyes, P.J. Bushnell, J.H. Raymer, T. Limsakun, A. McDonald, Y.M. Sey, and M.V. Evans. 2002. A physiologically based pharmacokinetic model for trichloroethylene in the male long-evans rat. Toxicol. Sci. 69(1):3-15.

Sina, J.F., C.L. Bean, G.R. Dysar, V.I. Taylor, and M.O. Bradley. 1983. Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. Mutat. Res. 113(5):357-391.

Smyth, H.F., C.P. Carpenter, C.S. Weil, U.C. Pozzani, J.A. Striegel, and J.S. Nycum. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30(5):470-476.

Snow, L., P. MacNair, and B.C. Casto. 1981. Mutagenesis Testing of Toluene in Salmonella Strains TA100 and TA98. Prepared by Northrop Services, Inc., for U.S. Environmental Protection Agency, Research Triangle Park, NC.

Spanggord, R.J., K.E. Mortelmans, A.F. Griffin, and V.F. Simmon. 1982. Mutagenicity in *Salmonella typhimurium* and structure-activity relationships of wastewater components emanating from the manufacture of trinitrotoluene. Environ. Mutagen. 4(2):163-179.

Stevens, W.C., W.M. Dolan, R.T. Gibbons, A. White, E.I. Eger, R. 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.

Stewart, R.D., C.L. Hake, H.V. Forster, A.J. Lebrun, J.E. Peterson, and A.Wu. 1975. Toluene: Development of a Biologic Standard for the Industrial Worker by Breath Analysis. NIOSH-00080663. PB-82154220. National Institute for Occupational Safety and Health, Cincinnati, OH.

Streicher, H.Z., P.A. Gabow, A.H. Moss,, D. Kono, and W.D. Kaehny. 1981. Syndromes of toluene sniffing in adults. Ann. Int. Med. 94(6):758-762.

Suzuki, H. 1973. Autonomic nervous responses to experimental toluene exposure in humans [in Japanese]. Sangyo Igaku 15:379-384.

Svensson, B.G., G. Nise, V. Englander, R. Attewell, S. Skerfving, and T. Moller. 1990. Deaths and tumours among rotogravure printers exposed to toluene. Br. J. Ind. Med. 47(6):372-379.

Svensson, B.G., G. Nise, E.M. Erfurth, A. Nilsson, and S. Skerfving. 1992. Hormone status in occupational toluene exposure. Am. J. Ind. Med. 22(1):99-107.

Svirbely, J.L., R.C. Dunn, and W.F. von Oettingen. 1943. The acute toxicity of vapors of certain solvents containing appreciable amounts of benzene and toluene. J. Ind. Hyg. Toxicol. 25(8):366-373.

Taher, S.M., R.J. Anderson, R. McCartney, M. Popovtzer, and R.W. Schrier. 1974. Renal tubular acidosis associated with toluene sniffing. N. Engl. J. Med. 290:765-768.

Takeichi, S., T. Yamada, and I. Shikata. 1986. Acute toluene poisoning during painting. Forensic Sci. Int. 32(2):109-115.

Takeuchi, T., and N. Hisanaga. 1977. The neurotoxicity of toluene: EEG changes in rats exposed to various concentrations. Br. J. Ind. Med. 34(4):314-324.

Tanaka, K., T. Maeda, T. Kobayashi, M. Tanaka, and T. Fukushima. 2003. A survey of urinary hippuric acid and subjective symptoms among occupational low toluene exposed workers. Fukushima J. Med. Sci. 49(2):129-139.

Tardif, R., S. Lapare, G.L. Plaa, and J. Brodeur. 1991. Effect of simultaneous exposure to toluene and xylene on their respective biological exposure indices in humans. Int. Arch. Occup. Health 63(4):279-284.

Tardif, R., G.L. Plaa, and J. Brodeur. 1992. Influence of various mixtures of inhaled toluene and xylene on the biological monitoring of exposure of these solvents in rats. Can. J. Physiol. Pharmacol. 70(3):385-393.

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

Tardif, R., S. Lapare, G. Charest-Tardif, J. Brodeur, and K. Krishnan. 1995. Physiologically-based pharmacokinetic modeling of a mixture of toluene and xylene in humans. Risk. Anal. 15(3):335-342.

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.

Tardif, R., P.O. Droz, G. Charest-Tardif, G. Pierrehumbert, and G. Truchon. 2002. Impact of human variability on the biological monitoring of exposure to toluene: I. Physiologically based toxicokinetic modelling. Toxicol. Lett. 134(1-3):155-163.

Tatrai, E., K. Rodics, and G.Y. Ungvary. 1980. Embryotoxic effects of simultaneously applied exposure of benzene and toluene. Folia Morphol. (Praha) 28(3):286-289.

Taylor, J.D., and H.L. Evans. 1985. Effects of toluene inhalation on behavior and expired carbon dioxide in macaque monkeys. Toxicol. App. Pharmacol. 80(3):487-495.

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.

ten Berge, W.F., A. Zwart, and L.M. Appelman. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Mater. 13(3):301-309.

Thiel, R., and I. Chahoud. 1997. Postnatal development and behavior of Wistar rats after prenatal toluene exposure. Arch. Toxicol. 71:258-265.

Thrall, K.D., R.A. Gies, J. Muniz, A.D. Woodstock, and G. Higgins. 2002. Route-ofentry and brain tissue partition coefficients for common superfund contaminants. J. Toxicol. Environ. Health A 65(24):2075-2086.

Tice, R.R., T.F. Vogt, and D.L. Costa. 1982. Cytogenic effects of inhaled benzene in murine bone marrow. Environ. Sci. Res. 25:257-275.

Topham, J.C. 1980. Do induced sperm-head abnormalities in mice specifically identify mammalian mutagens rather than carcinogens? Mutat. Res. 74(5):379-387.

Ukai, H., T. Watanabe, H. Nakatsuka, T. Satoh, S.J. Liu, X. Qiao, Y. Hong, C. Jin, G.L. Li, and M. Ikeda. 1993. Dose-dependent increase in subjective symptoms among toluene-exposed workers. Environ. Res. 60(2):274-289.

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

U.S. Air Force. 1989. Equilibrium partitioning calculations for toluene in model environments. Pp. 19-1 to 19-37 in The Air Force Installation Restoration Program Toxicology Guide, Vol. 2. Wright-Patterson Air Force Base, OH.

van Asperen, J., W.R. Pels Rijcken, V.J. Feron, and J.H.C.M. Lammers. 2002. Physiologically-Based Toxicokinetic Modelling of Peak Exposure Versus Constant Exposure to Toluene in the Rat. Poster Presented at the Society of Toxicology Meeting, March 17-21, 2002, Nashville, TN.

van Asperen, J., W.R. Rijcken, and J.H. Lammers. 2003. Application of physiologically based toxicokinetic modelling to study the impact of the exposure scenario on the toxicokinetics and the behavioural effects of toluene in rats. Toxicol. Lett. 138(12):51-62.

Veulemans, H., and R. Masschelein. 1978. Experimental human exposure to toluene. II. Toluene in venous blood during and after exposure. Int. Arch. Occup. Environ. Health 42(2):105-117.

Vicini, P., C.H. Pierce, R.L. Dills, M.S. Morgan and D.A. Kalman. 1999. Individual prior information in a physiological model of 2H8-toluene kinetics: An empirical Bayes estimation strategy. Risk. Anal. 19(6):1127-1134.

Vidrio, H., G.A. Magos, and M. Lorenzana-Jones. 1986. Electrocardiographic effects of toluene in the anesthetized rat. Arch. Int. Pharmacodyn. 279(1):121-129.

von Oettingen, W.F., P.A. Neal, and D.D. Donahue. 1942. The toxicity and potential dangers of toluene with special reference to its maximal permissible concentration. J. Am. Med. Assoc. 118(8):579-584.

Vrca, A., D. Bozicevic, V. Karacic, R. Fuchs, D. Prpic-Majic, and M. Malinar. 1995. Visual evoked potentials in individuals exposed to long-term low concentrations of toluene. Arch. Toxicol. 69(5):337-340.

Wada, H., T. Hosokawa, and K. Saito. 1989. Single toluene exposure and changes of response latency in shock avoidance performance. Neurotoxicol. Teratol. 11(3):265-272.

Waldron, H.A., N. Cherry, and J.D. Johnson. 1983. The effects of ethanol on blood toluene concentrations. Int. Arch. Occup. Environ. Health 51(4):365-369.

Wallen, M., S. Holm, and M. Nordqvist. 1985. Coexposure to toluene and p-xylene in man: Uptake and elimination. Br. J. Ind. Med. 42(2):111-116.

Wang, R.S., T. Nakajima, and S.S. Park. 1993. Monoclonal antibody-directed assessment of toluene induction of rat hepatic cytochrome P450 isozymes. Biochem. Pharmacol. 46(3):413-419.

Weisenberger, B.L. 1977. Toluene habituation. J. Occup. Med. 19(8):569-570.

Weiss, B., R.W. Wood, and D.A. Macys. 1979. Behavioral toxicology of carbon disulfide and toluene. Environ. Health Perspect. 30:39-45.

Weiss, G. 1980. Toluene. P. 870 in Hazardous Chemicals Data Book. Park Ridge NJ: Noyes Data Corporation.

WHO (World Health Organization). 1985. Toluene. Environmental Health Criteria 52. Geneva: World Health Organization [online]. Available: http://www.inchem.org/documents/ehc/ehc/ehc52.htm [accessed Apr. 5, 2014].

WHO (World Health Organization). 1987. Toluene. Pp. 137-147 in Air Quality Guidelines for Europe. WHO Regional Publications, European Series 21. Copenhagen, Denmark: World Health Organization.

Wilson, R.H. 1943. Toluene poisoning. J. Am. Med. Assoc. 123(17):1106-1109.

Winneke, G. 1982. Acute behavioral effects of exposure to some organic solvents - psychophysiological aspects. Acta Neurol. Scand. 92 (suppl.):117-129.

Wiseman, M.N., and S. Banim. 1987. "Glue sniffer's" heart? Br. Med. J 294(6574):739.

Wood, R., and C. Cox. 1995. A repeated measures approach to the detection of the acute behavioral effects of toluene at low concentrations. Fundam. Appl. Toxicol. 25(2):293-301.

Wood, R.W., D.C. Rees, and V.G. Laties. 1983. Behavioral effects of toluene are modulated by stimulus control. Toxicol. Appl. Pharmacol. 68(3):462-472.

Wood, R., J.B. Coleman, R. Schuler, and C. Cox. 1984. Anticonvulsant and antipunishment effects of toluene. J. Pharmacol. Exp. Ther. 230(2):407-412.

Yin, S., G. Li, Y. Hu, X. Zhang, C. Jin, O. Inoue, K. Seiji, M. Kasahara, H. Nakatsuka, and M. Ikeda. 1987. Symptoms and signs of workers exposed to benzene, toluene or the combination. Ind. Health 25(3):113-130.

Zavalic, M., Z. Mandic, R. Turk, A. Bogadi-Sare, and D. Plavec. 1998. Quantitative assessments of color vision impairment in workers exposed to toluene. Am. J. Ind. Med. 33(3):297-304.

APPENDIX A

DERIVATION OF AEGL VALUES FOR TOLUENE

Derivation of AEGL-1 Values

Key studies:

Astrand, I., H. Ehrner-Samuel, A. Kilbom, and P. Ovrum. 1972. Toluene exposure. I. Concentration in alveolar air and blood at rest and during exercise. Scand. Work Environ. Health 9:119-130.

Baelum J., I. Andersen, G.R. Lundqvist, L. Mohave, O. F. Pedersen, M. Vaeth, and D.P. Wyon. 1985. Response of solvent-exposed printers and unexposed controls to six-hour toluene exposure. Scand. J. Work Environ. Health 11(4):271-280.

Baelum, J., G.R. Lundqvist, L. Molhave, and N.T. Andersen. 1990. Human response to varying concentrations of toluene. Int. Arch. Occup. Environ. Health 62(1):65-72.

Dick, R.B., J.V. Setzer, R. Wait, R., M.B. Hayden, B.J. Taylor, B. Tolos, and V. Putz-Anderson. 1984. Effects of acute exposure of toluene and methyl ethyl ketone on psychomotor performance. Int. Arch. Occup. Environ. Health 54(2):91-109.

Echeverria, D., L. Fine, G. Langolf, A. Schork, and C. Sampaio. 1989. Acute neurobehavioral effects of toluene. Br.. J Ind. Med. 46(7):483-495.

Echeverria, D., L. Fine, G. Langolf, T. Schork, and C. Sampaio. 1991. Acute behavioral comparisons of toluene and ethanol in human subjects. Br.. J. Ind. Med. 48(11):750-761.

Gamberale, F., and M. Hultengren. 1972. Toluene exposure. II. Psychophysiological functions. Work Environ. Health 9(3):131-139.

Nielsen, H.K., L. Krusell, J. Baelum, G. Lundqvist, G. O. Omland, M. Vaeth, M., S.E. Husted, C.E. Mogensen, and E. Geday. 1985. Renal effects of acute exposure to toluene. Acta Med. Scand. 218(3):317-321.

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

Stewart, R.D., C.L. Hake, H.V. Forster, and A.J. Lebrun. 1975. Toluene: development of a biologic standard for the industrial worker by breath analysis. NIOSH-00080663; National Institute for OccupationalSafety and Health, Cincinnati, OH.

Toxicity end point:	200 ppm for short- and long-exposure durations; effects would not exceed the definition of an AEGL-1
Time scaling:	None applied; toluene rapidly approaches steady-state in the blood at low concentrations.
Uncertainty factors:	3 for intraspecies variability; the minimum alveolar concentration for volatile anesthetics differs by no more than 2- to 3-fold in the human population.
10-min AEGL-1:	200 ppm ÷ 3 = 67 ppm
30 min AEGL-1:	200 ppm ÷ 3 = 67 ppm
1-h AEGL-1:	200 ppm ÷ 3 = 67 ppm
4-h AEGL-1:	200 ppm ÷ 3 = 67 ppm

8-h AEGL-1:	200 ppm ÷ 3 = 67 ppm

Derivation of AEGL-2 Values

Key studies:	Bushnell, P.J., W.M. Oshiro, T.E. Samsam, V.A. Benignus, Q.T. Krantz, and E.M. Kenyon. 2007a. A dosimetric analysis of the acute behavioral effects of inhaled toluene in rats. Toxicol. Sci. 99(1):181-189.
Toxicity end point:	No-observed-adverse-effect level of 1,600 ppm for 34 min based on doubling of reaction time in rats; concentration-related decrease in accuracy and increase in response time in a signal detection task with food reward.
Time scaling:	CNS effects observed after toluene exposure were assumed to be directly related to parent material reaching the brain. Therefore, a physiologically-based pharmacokinetic (PBPK) model for the rat (see Appendix C) was used to calculate the internal dose (BrTC) correlating with the exposure. A human PBPK model was then used determine the equivalent exposure concentration that would produce the target BrTC in humans at each AEGL duration.
Uncertainty factors:	1 for interspecies differences; PBPK modeling allows a comparison of the internal dose in both rats and humans from identical external exposures, and similar CNS effects were observed in rodents and humans. 3 for intraspecies variability; the minimum alveolar concentration for volatile anesthetics differs by no more than 2- to 3-fold in the human population.
10-min AEGL-2:	1,400 ppm (based on results of PBPK model)
30-min AEGL-2:	760 ppm (based on results of PBPK model)
1-h AEGL-2:	560 ppm (based on results of PBPK model)
4-h AEGL-2:	310 ppm (based on results of PBPK model)

8-h AEGL-2:	250 ppm (based on results of PBPK model)

Derivation of AEGL-3 Values

Key study:	Mullin, L.S. and N.D. Krivanek. 1982. Comparison of unconditioned reflex and conditioned avoidance tests in rats exposure by inhalation to carbon monoxide, 1,1,1trichloroethane, toluene or ethanol. Neurotoxicity 3(1):126-137.
Toxicity end point:	Threshold for lethality in rats of 6,250 ppm for 2 h
Time scaling:	CNS effects observed after toluene exposure were assumed to be directly related to parent material reaching the brain. Therefore, a PBPK model for the rat (see Appendix C) was used to calculate the internal dose (BrTC) correlating with the exposure. A human PBPK model was then used determine the equivalent exposure concentration that would produce the target BrTC in humans at each AEGL duration.
Uncertainty factors:	1 for interspecies differences; PBPK modeling allows a comparison of the internal dose in both rats and humans from identical external exposures, and similar CNS effects were observed in rodents and humans. 3 for intraspecies variability; the minimum alveolar concentration for volatile anesthetics differs by no more than 2- to 3-fold in the human population.
10-min AEGL-3:	10,000 ppm (based on results of PBPK model)
30-min AEGL-3:	5,200 ppm (based on results of PBPK model)
1-h AEGL-3:	3,700 ppm (based on results of PBPK model)
4-h AEGL-3:	1,800 ppm (based on results of PBPK model)
8-h AEGL-3:	1,400 ppm (based on results of PBPK model)

APPENDIX B

CATEGORY PLOT FOR TOLUENE

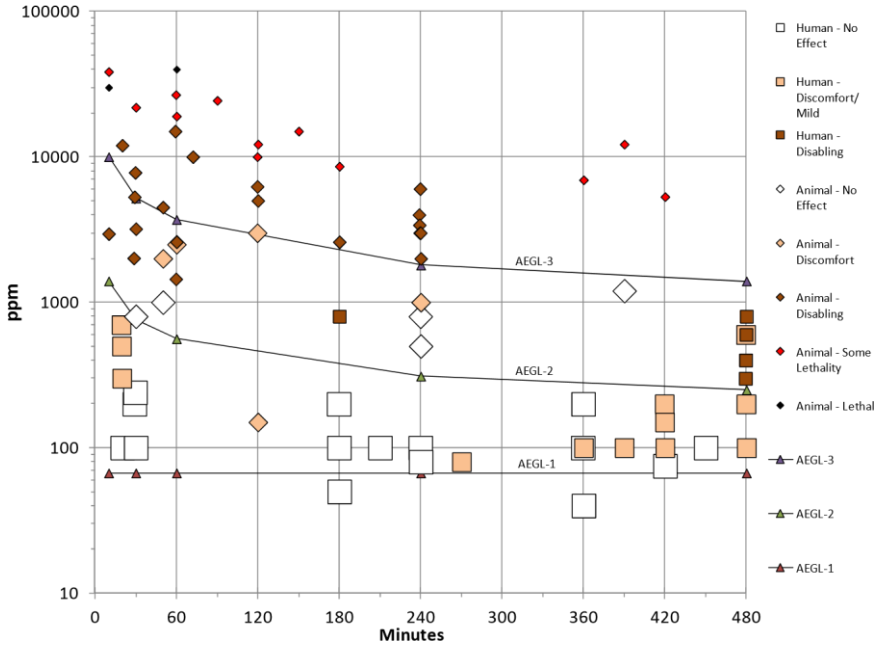

FIGURE B-1 Category plot of animal toxicity data and AEGL values for toluene.

TABLE B-1 Data Used in Category Plot for Toluene

Source	Species	ppm	Minutes	Category
AEGL-1		67	10	AEGL
AEGL-1		67	30	AEGL
AEGL-1		67	60	AEGL
AEGL-1		67	240	AEGL
AEGL-1		67	480	AEGL
AEGL-2		1,400	10	AEGL
AEGL-2		760	30	AEGL
AEGL-2		560	60	AEGL
AEGL-2		310	240	AEGL
AEGL-2		250	480	AEGL
AEGL-3		10,000	10	AEGL
AEGL-3		5,200	30	AEGL
AEGL-3		3,700	60	AEGL
AEGL-3		1,800	240	AEGL
AEGL-3		1,400	480	AEGL
Andersen et al. 1983	Human	40	360	0, no neurobehavioral effects
Andersen et al. 1983	Human	100	360	1, slight ocular and nasal irritation; no neurobehavioral effects
Cherry et al. 1983; Olson et al. 1985	Human	80	240	0, no neurobehavioral effects
Iregren et al. 1986	Human	80	270	1, subjective symptoms

(Continued)

TABLE B-1 Continued

Source				Category	
Species		ppm			Minutes
Winneke 1982	Human	100	210	0, no behavioral deficits in psychomotor tests	
Dick et al. 1984	Human	100	240	0, no neurobehavioral deficits	
Rahill et al. 1996	Human	100	360	0, slight latency, neurobehavioral tests	
Baelum et al. 1985	Human	100	390	1, sensory irritation, sleepiness, behavioral deficits	
Stewart et al. 1975	Human	100	450	0, no neurobehavioral deficits	
Baelum et al. 1990	Human	100	420	1, sensory irritation	
Echeverria et al. 1989	Human	75	420	0, no neurobehavioral effects	
Echeverria et al. 1989	Human	150	420	1, ocular irritation, headache	
Astrand et al. 1972	Human	100	30	0, no neurobehavioral effects	
Astrand et al. 1972	Human	200	30	0, no neurobehavioral effects with exercise	
Ogata et al. 1970	Human	100	180	0, no effects	
Ogata et al. 1970	Human	200	180	0, no effects	
von Oettingen et al. 1942	Human	100	480	1, moderate fatigue	
von Oettingen et al. 1942	Human	300	480	2, increasing fatigue symptoms	
von Oettingen et al. 1942	Human	400	480	2, increasing fatigue symptoms	
von Oettingen et al. 1942	Human	600	480	2, increasing fatigue symptoms	
von Oettingen et al. 1942	Human	800	180	2, incoordination	
Gamberale and Hultengren 1972	Human	100	20	0, no effect on reaction time	
Gamberale and Hultengren 1972	Human	300	20	0, increase in reaction time	
Gamberale and Hultengren 1972	Human	500	20	0, increase in complex reaction time	
Gamberale and Hultengren 1972	Human	700	20	0, decrease in perceptual speed at end of exposure	
Carpenter et al. 1944	Human	200	420	1, mild irritation	

Carpenter et al. 1944	Human	400	420	1, mild ocular irritation
Carpenter et al. 1944	Human	600	480	1, lassitude
Carpenter et al. 1944	Human	800	480	2, inebriation
Suzuki 1973	Human	200	360	0, no effect
Horvath et al. 1981	Human	240	30	0, no effect
von Oettingen et al.	Human	200	480	1, mild discomfort
Luderer et al 1999	Human	50	180	0, no symptoms
Pryor et al. 1978	Rat	26,700	60	SL, LC_{50}
Cameron et al. 1938	Rat	24,400	90	SL, 60% mortality
Cameron et al. 1938	Rat	12,200	390	SL, LC_{50}
Kojima and Kobayashi 1973	Rat	15,000	150	SL, 80% mortality
Kojima and Kobayashi 1973	Rat	12,200	120	SL, LC_{50}
Kojima and Kobayashi 1973	Rat	5,000	120	2, no mortality
Mullin and Krivanek 1982	Rat	6,250	120	2, no mortality
Moser and Balster 1985	Mouse	38,465	10	SL, LC_{50}
Moser and Balster 1985	Mouse	21,872	30	SL, LC_{50}

TABLE B-1 Continued

Source			Minutes	
Species		ppm		Category
Moser and Balster 1985	Mouse	19,018	60	SL, LC_{50}
Bruckner and Peterson 1981a	Mouse	12,000	20	2, no mortality
Bruckner and Peterson 1981a	Mouse	8,600	180	SL, LC_{50}
Bonnet et al. 1979	Mouse	6,940	360	SL, LC_{50}
Svirbely et al. 1943	Mouse	5,320	420	SL, LC_{50}
Bruckner and Peterson 1981a	Mouse	2,600	180	2, immobility in absence of stimulus
NTP 1990	Rat, mouse	1,200	390	0, no clinical signs

Moser and Balster 1985	Mouse	2,959	10	2, EC_{50}, inverted screen test
Moser and Balster 1985	Mouse	2,012	30	2, EC_{50}, inverted screen test
Moser and Balster 1985	Mouse	1,445	60	2, EC_{50}, inverted screen test
Moser and Balster 1981	Mouse	3,200	30	2, ataxia
Bruckner and Peterson 1981a	Mouse	2,600	60	2, ataxia
Glowa 1981	Mouse	500	240	0, no effects, scheduled controlled behavior
Glowa 1981; Takeuchi and Hisanga 1977	Mouse	2,000	240	2, changes in behavior
Shigeta et al. 1978; Takeuchi and Hisanaga 1977	Rat	1,000	240	1, no changes in behavior
Shigata et al. 1978	Rat	3,000	240	2, changes in avoidance response, ataxia
Hinman 1987	Mouse	2,500	60	1, no effect on motor activity
Mullin and Krivanek 1982	Mouse	800	240	0, threshold, unconditioned reflex change
Miyagawa et al. 1986	Rat	3,400	240	2, 31% activity decrease
Geller et al. 1979	Rat	150	120	1, reduced neurobehavioral performance
Hinman 1987	Rat	15,000	60	2, no mortality
Nielsen and Alarie 1982	Mouse	7,800	30	2, no mortality
Nielsen and Alarie 1982	Mouse	5,300	30	2, RD_{50}
Kojima and Kobayashi 1973	Rat	10,000	120	SL, 20% mortality
Pryor et al. 1978	Rat	40,000	60	3, lethal
Ikeda et al 1990	Dog	30,000	10	3, lethal
Kishi et al. 1988	Rat	4,000	240	2, ataxia
Taylor and Evans 1985	Monkey	1,000	50	0, no effect
Taylor and Evans 1985	Monkey	2,000	50	1, impairment, cognitive function
Taylor and Evans 1985	Monkey	4 500	50	2, failure to respond in cognitive function test
Wood and Cox 1995	Rat	3,000	120	1, increased activity
Wood et al. 1984	Rat	3,000	240	2, ataxia
Bushnell et al. 1985	Mouse	10,000	72	2, decrease in activity

Moser and Balster 1981	Mouse	800	30	0, no change in operant behavior
Wada et a. 1989	Rat	6,030	240	2, no mortality

For category: 0 = no effect, 1 = discomfort, 2 = disabling, SL = some lethality, 3 = lethal

APPENDIX C

PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELING OF TOLUENE

Summary

The method used in this appendix to determine human equivalent AEGL values is similar to that previously reported (Bruckner et al. 2004; Krewski et al. 2004) and follows the methodology described in the PBPK Modeling White Paper, Addressing the Use of PBPK Models to Support Derivation of Acute Exposure Guideline Levels (AEGLs), (Dennison et al. 2010). The method reduces the uncertainty inherent in extrapolating rat toxicity data to humans and extrapolating toxicity data across time scales, by using validated PBPK models to perform the extrapolation based on an internal measure of dose. This reduces the uncertainty in the pharmacokinetic component of the extrapolation. Uncertainty in the pharmacodynamic component of the rat-tohuman extrapolation is handled with standard uncertainty factors.

The end points found in the critical studies for AEGL 2 and AEGL 3 values can be reasonably associated with the blood concentration of toluene. The blood concentration is a superior measure of dose than the applied concentration (exposure concentration) because, as an internal measure of dose, pharmacokinetic alterations in tissue dosimetry are addressed in extrapolations by explicit quantification. In an extrapolation, for example, of a 1-h AEGL to an 8-h AEGL, the increase in blood concentration over time is explicitly compensated for by reducing the 8-h AEGL to the point where blood concentrations are equivalent. This obviates the need for the use of algorithms such as the ten Berge et al. (1986) equation, which can result in corresponding errors when the empirical parameters are unknown.

Fundamentally, the PBPK-based AEGL values are based on the same critical studies as the AEGL values established in the technical support document; only the method of extrapolating from rat to human (dosimetry replaces pharmacokinetic uncertainty factors) and over time (dosimetry replaces empirical formulas) differs. When the PBPK-based approach replaces pharmacokinetic uncertainty factors, the resulting AEGL value may be higher due to the reduction in the total uncertainty factor.

The AEGL 1 value for toluene was based on effects that could not feasibly be modeled, so modeling was not applied. Modeling was performed in deriving the AEGL-2 and AEGL-3 values. The PBPK assessment method involves the following specific steps:

Step 1) Determine an appropriate dose metric, the pharmacokinetic measure of internal dose that correlates with the critical effect. For toluene, the critical effect is CNS depression, and a dose metric of peak concentration of toluene in brain (BrTC) was used.

Step 2) Develop a PBPK model for that chemical that adequately describes the pharmacokinetics of toluene in rats and humans with respect to CV. Describe model equations, parameter value development, and evaluation using experimental data from the literature.

Step 3) Calculate the dose metric amount under conditions that correspond to the critical study. For example, for toluene's AEGL 3 values, the critical study point of departure was 6,250 ppm for 2 h in rats. Based on the PBPK model, the CV in rats is 165 mg/L (at 2 h and 6,250 ppm).

Step 4) Apply the uncertainty factors determined in the technical support document to the dose metric. For AEGL-3 values, the total uncertainty factor was 3, for intraspecies variability. As described in the technical support document, the interspecies factor was set at 1, for a total uncertainty factor of 3. This total uncertainty factor may have been higher if PBPK modeling was not used. After application of the uncertainty factor of 3, the target internal dose of CV becomes 55 mg/L for AEGL 3. The uncertainty factor can also be applied after derivation of the human equivalent concentration (HEC) as an alternative, and in the derivation section of this appendix, both approaches are provided.

Step 5) Scale the model to humans by changing body weight and other parameter values to human values.

Step 6) Run the PBPK model to determine the HEC that corresponds to the target internal dose of 55 mg/L for each AEGL.

This appendix has three parts. First, the structure and parameterization of the toluene PBPK model is described. Second, validation of the model is provided by showing model performance against rat and human data sets obtained from the literature. Third, derivation of recommended AEGL values is performed.

Introduction

The critical studies that provide the NOAEL used in this analysis (Table C-1) are the same as those used in the technical support document to calculate AEGL values. For the AEGL-2 values, both a clinical study and a study with rats were considered. The study with rats was chosen as the basis for the AEGL-2 values, because the effect in this study, threshold for narcosis, more closely meets the definition of the AEGL-2. Supporting studies were not used in any of the AEGL calculations.

TABLE C-1 Critical Studies for Deriving AEGL Values for Toluene

Level	Study	Species	NOAEL	Duration
AEGL-2	Gamberale et al. 1972	Human	700 ppm[a]	20 min
AEGL-2	Bushnell et al. 2007a	Rat	1,600 ppm	34 min
AEGL-3	Mullin and Krivanek 1982	Rat	6,250	2 h

[a] After initial exposures at 100-500 ppm.

Additional information and justification of these choices of critical studies is available in the technical support document. The target tissue dose (venous blood concentration) was determined from these studies.

Selection of the Dose Metric

The dose metric used for the PBPK-based assessment is the concentration of toluene in the brain (BrTC). The critical effect of toluene for the setting of AEGLs has been determined to be CNS depression, on the basis of toxicity studies presented in the technical support document. It has been generally suggested that CNS depression caused by organic solvents, such as toluene, is mediated by the action of the parent chemical and not metabolites (Bruckner and Warren 2001). The concentration of toluene in that target brain tissue is proportional to the concentration in venous blood (van Asperen et al. 2003) once steady state has been achieved. The PBPK models have been parameterized to provide CV as model output under the exposure conditions indicated for this assessment.

Model Selection

The present approach requires a validated PBPK model for rats and humans. Three options exist for developing or selecting a model to use: 1) develop a wholly new model, 2) modify an existing model, or 3) select an existing model and use in its present form. If an existing model would serve the needs of this assessment, option #3 is the preferred choice and was the first approach to be used. Ultimately, an existing model was used with minor modifications.

An evaluation of all existing models can in principle be performed to determine the best available model. However, this process is time consuming and can be arbitrary to some extent. Therefore, the method of selecting a model was to screen models for good candidates using specific criteria, and evaluate models one by one until an acceptable model was identified. The criteria used to screen models included: 1) the model should include the inhalation route of exposure (primarily), 2) development of the model should incorporate validation against venous blood data, 3) the model should be reported in the peer reviewed literature, and 4) the model should have as a primary purpose the goal of rat-to-human extrapolation.

A number of PBPK models have published for inhalation of toluene (Purcell et al. 1990; Tardif et al. 1993; Pierce et al. 1996a; Tardif et al. 1997; Benignus et al. 1998; Pierce et al. 1998; Ali and Tardif 1999; Haddad et al. 1999a; Pierce et al. 1999; Vicini

et al. 1999; Jonsson et al. 2001; Tardif et al. 2002; van Asperen et al. 2003; Benignus et al. 2006; Kenyon et al. 2008). Several of these are variations of each other. Some were developed for rats, others for humans, and some for both (with modification of appropriate parameter values). The purpose for some of the models was evaluation of mixture interactions, although in each of these cases, a model was first developed for toluene as a single chemical. The two most recently published models that met the criteria described above are those of Kenyon et al.
(2008) for the rat and that of Benignus et al. (2006) for the human.

Model Structure

The model structure is shown in Figure C-1. The tissue groups/compartments specified are consistent with models for other inhaled volatile organic solvents (Reddy et al. 2005). The individual compartments (lungs, brain, liver, gastrointestinal tissue, fat, and slowly and rapidly perfused tissue groups) are connected by the systemic circulation. The model has distinct arterial and venous blood compartments and tissues are described as homogeneous well-mixed compartments. Metabolism is described by a single metabolic pathway following saturable (Michaelis-Menten) kinetics in the liver. Brain is the target tissue of interest and fat is a major site for sequestration.

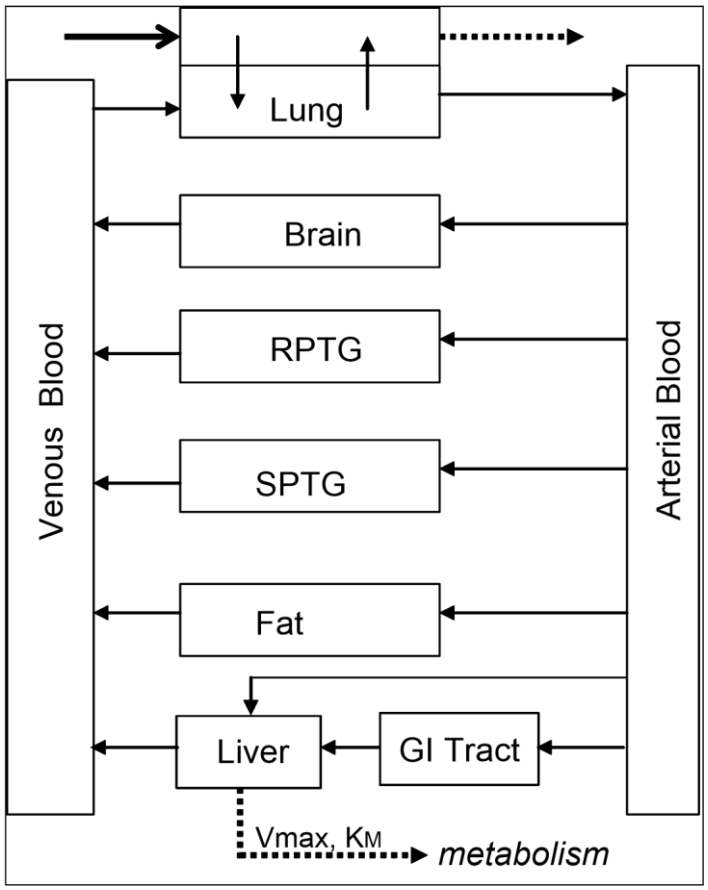

FIGURE C-1 Schematic diagram of the toluene PBPK model. Source: Kenyon et al. 2008. Reprinted with permission; copyright 2008, *Journal of Toxicology and Environmental Health, Part A: Current Issues*.

TABLE C-2 Physiologic Parameters for the Toluene Rat Model

Parameter, units	Symbol	Value	Footnote
Body weight, kg	BW	0.237-0.508	*1*
Cardiac output, L/h-kg$^{0.75}$	QCC		*2*
Normal		11.2	
Sedentary, day acclimated		11.2	
Active, day-acclimated		13.2	
Alveolar ventilation, L/h-kg$^{0.75}$	QPC		*2*
Normal		9.9	Ratio = 0.9
Sedentary, day-acclimated		12.2	Ratio = 1.1

Active, day-acclimated		22.4	Ratio = 1.7
Flow (fraction QC)[3]			
Lung	QCC	1.0	[4]
Liver	QLC	0.02	
Fat	QFC	0.082	
Brain	QBC	0.027	
Gut	QGC	0.16	
SPTG	QSC	0.257	
RPTG	QRC	1-□Qi	
Volumes (fraction body weight)[5]			
Arterial blood	VABC	0.030	
Venous blood	VVBC	0.060	
Lung	VNC	0.0048	
Liver	VLC	0.0401	
Fat	VFC	0.08-0.16	[6]
Brain	VBC	0.0054	
Gut	VGC	0.0249	
SPTG	VSC	0.60	
RPTG	VRC	1-□Vi	

[1] Body weight is an experiment-specific measurement.

[2] Experiment-specific based on type of acclimation and activity level of rat. "Normal" refers to rats with a normal diurnal cycle of being active and fed at night and studied during daylight hours, whether weight-maintained or free-fed. "Sedentary, dayacclimated" refers to rats acclimated to be fed and active during the light part of their diurnal cycle, but not performing a task. "Active, day-acclimated" refers to rats acclimated to be fed and active during the light part of their diurnal cycle and performing a lever pressing task. Ratio is the ratio of QPC/QCC, an approximation of ventilation-perfusion ratio. [3] Values are from two main sources (Brown et al. 1997; Simmons et al. 2002).

[4] Lung receives all of cardiac output.

[5] Values that LE rat specific were calculated from regression equations (Simmons et al. 2002) for a 0.35 kg rat. Other values are from a standard reference (Brown et al.

1997). All calculated values were checked against reported ranges of reference values (Brown et al. 1997). [6] Experiment-specific based on body weight of rat using regression equation from Simmons et al. (2002).

TABLE C-3 Chemical-Specific Parameters for the Toluene Rat Model

Parameter	Symbol	Units	Value	Reference
Partition coefficients				
Blood:air	PB	None	21.0	Thrall et al. 2002
Lung:blood	PN	None	1.14	
Liver:blood	PL	None	2.01	
Brain:blood	PBR	None	1.72	
Fat:blood	PF	None	86.19	
Gut:blood	PG	None	2.62	
RPTG:blood	PR	None	2.62	
SPTG:blood	PS	None	1.32	
Metabolism parameters				
V_{max}	VMAXC	$L/h/kg^{0.75}$	4.55	Tardif et al. 1993[a]
K_M	KM	mg/L	0.45	

[a] Metabolism parameters are consistent with the range of published values in the literature (DeJongh and Blaauboer 1996).

Physiological and Chemical-Specific Parameter Values

Physiological and chemical-specific parameter values used in the present model for rats are listed in Tables C-2 and C-3, respectively. Model code is provided in Attachment 1. All details concerning model calibration and evaluation for both the rat model and the human GPAT model can be obtained from the original publications (Benignus et al. 2006; Kenyon et al. 2008).

Derivation of AEGLs with PBPK-Based Approach

The AEGL-2 critical study was Bushnell et al. (2007a), in which the NOAEL for a doubling in choice reaction time in Long-Evans rats exposed to toluene was 1,600 ppm for 34 min. As shown in Table C-4, the internal dose metric of brain toluene concentration (BrTC) in the rat was determined using a PBPK model (Kenyon et al. 2008), and the determination of the HEC used the human GPAT model (Benignus et

al. 2006). The BrTC in rats at the end of exposure, calculated by the PBPK model, was 49.2 mg/L. A total uncertainty factor of 3 was applied to the rat BrTC to arrive at the target internal dose in humans of 16.4 mg/L. The uncertainty factor of 3 was applied to the internal dose metric, as recommended by the Standing Operating Procedures (NRC 2001), to arrive at final human exposure values in the final row of Table C-4 which were rounded to obtain the final AEGL-2 values. The AEGL-2 values were also compared to the estimated toluene exposure concentrations (ppm) which would lead to decrements in reaction time similar to those associated with ethanol inebriation (0.08% and 0.10% blood ethanol level), with the AEGL-2 values are between those two estimates (lower portion of Table C-4).

TABLE C-4 Toluene Concentrations in Air Associated with Relevant Brain Toluene Concentrations in Rats and Humans as Determined by PBPK Modeling

	10 min	30 min	1 h	4 h	8 h
Duration extrapolation at the critical brain toluene concentration (BrTC) in rats, and extrapolation to humans using one-third of the critical internal dose (per guidance in NRC 2002)					
Rat internal dose metric (1,600 ppm 651 ppm for 34 min) ; BrTC = 49.2 mg/L	3,085 ppm	1,705 ppm	1,243 ppm		809 ppm
AEGL-2 values based on GPAT estimates in humans; BrTC = (49.2/3) = 16.4 mg/L	1,396 ppm	757 ppm	558 ppm	311 ppm	251 ppm
Toluene concentrations leading to effect levels comparable to blood ethanol levels (BELs) of 0.08% and 0.10%					
GPAT estimations of exposures comparable to BEL of 0.08% (standing); BrTC = 119 µM = 10.9 mg/L	930 ppm	520 ppm	390 ppm	230 ppm	190 ppm
GPAT estimations of exposures comparable to BEL of 0.10% (standing); BrTC = 241 µM = 24.1 mg/L	1,860 ppm	1,000 ppm	730 ppm	390 ppm	320 ppm

Source: Based on Bushnell et al. 2007a.

For comparative purposes, alternative AEGL-2 values were also calculated using the clinical study of Gamberale and Hultengren (1972) as shown in Table C-5. In this study, the threshold for narcosis was not approached as indicated by the failure to produce significant deficits in tests of perceptual speed and reaction time. In the Gamberale and Hultengren (1972) study, subjects were sequentially exposed to toluene at 100, 300, 500, and 700 ppm for 20 min at each level, with a short break in the middle. The venous blood concentration calculated by the PBPK model is much greater when the full exposure regimen was simulated compared with the concentration after only a 20 min exposure (about 6.5 versus 4.5 mg/L). The actual exposures were roughly equivalent to a 20-min exposure at about 1,000 ppm.

Therefore, the CV determined for the actual experimental conditions was used to derive AEGL-2 values. According to the standing operating procedure for use of PBPK modeling in AEGL value development, the uncertainty factor can be applied to the HEC or to the dose metric of 6.54 mg/L, but the latter approach is generally preferred. If the total uncertainty factor is 1, the approaches become the same. The alternative AEGLs were deemed to be not as credible as the refined approach using the rat data extrapolated via the human GPAT model based on the comparisons with the toluene concentrations leading to effect levels comparable to blood ethanol levels of 0.08% and 0.10%, as shown in the lower portion of Table C-4.

TABLE C-5 AEGL-2 Values for Toluene Determined with PBPK Model of Human Data

	10 min	30 min	1 h	4 h	8 h
UF = 1	1,855	805	601	426	378
UF = 3, applied to human equivalent concentration	618	268	200	142	126
UF = 3, applied to dose metric	655	305	239	180	166

Source: Based on Gamberale and Hultengren 1972.

The AEGL-3 values were based on a rat NOAEL for lethality and were determined in the same manner as the AEGL-2 values: the determination of the internal dose metric used the rat PBPK model and the determination of the HEC used the human GPAT model. In Table C-6, the results in the first row are based on the target internal dose (BrTC) of 362 mg/L taken from the Mullin and Krivanek (1982) study in rats, then deriving the HEC with no adjustment with uncertainty factors using the GPAT model. In the second row, the HEC determined for an uncertainty factor of 1 (listed in the first row) were divided by 3. The results in the third row were obtained by dividing 362 mg/L by 3 (121 mg/L) as a new target internal dose, and then using the human GPAT model to determine the corresponding HECs.

TABLE C-6 Comparison of AEGL-3 Values for Toluene Determined by PBPK Modeling

	10 min	30 min	1 h	4 h	8 h
UF = 1, human BrTC = 362 mg/L	30,200 ppm	15,440 ppm	10,860 ppm	5,210 ppm	3,920 ppm
UF = 3, applied to human equivalent concentration	10,067 ppm	5,147 ppm	3,620 ppm	1,737 ppm	1,307 ppm
UF = 3, applied to dose metric	10,125 ppm	5,209 ppm	3,680 ppm	1,810 ppm	1,370 ppm

Source: Based on Mullin and Krivanek (1982), NOAEL for lethality of 6,250 ppm (2 h) in rats.

Attachment 1

PBPK Model Code for Toluene AEGL Rat Model

Models used were published models for the rat (Kenyon et al. 2008) and the human GPAT model (Benignus et al. 2006). All model calibration details and evaluation data and equations are available in these papers, except where otherwise noted (e.g., QPC and QCC values were set equal to 15 L/h-kg, so that the values for these highly influential parameters were equal to those used in the Dennison model originally used for AEGL derivation). The code below is for the Kenyon el. al. (2008) model realized in acslX 3.0.1.6 (Aegis Technologies Group, Austin, TX).

```
PROGRAM      TOLRAT1.CSL  !PBPK Model for Toluene (TOL)in rat
             !created by Elaina Kenyon 08/04/05
             !incl. explicit arterial and venous compt
             !& non-SS lung, both inhalation & oral routes

LOGICAL      TOLCHX
             !If TOLCHX = true, then check Toluene
             !mass balance
             TOLCHX = .TRUE.
LOGICAL      DPSITG
             !Integration control variable for
             !precision
             DPSITG = TRUE.

INITIAL      !STATEMENTS EXECUTED ONLY AT THE
             BEGINNING OF THE !SIMULATION, CONSTANT
             COMMANDS EXECUTED ONLY at BUILD

CONSTANT     LIMIT = 0.1   !Limit for unbal. cmpds when checking
             mass balance
CONSTANT     DUMMY = 0.00001

!***** Physiological Parameters ****

CONSTANT     QPC = 16.1        !Alveolar Ventilation Rate(l/hr-kg)
CONSTANT     QCC = 16.1        !Cardiac Output(l/hr-kg)
CONSTANT     QLC = 0.02        !Fract. Blood Flow to Liver
CONSTANT     QFC = 0.052       !Fract. Blood Flow to Fat
CONSTANT     QBC = 0.114       !Fract. Blood Flow to Brain
CONSTANT     QGC = 0.16        !Fract. Blood Flow to Gut
CONSTANT     QSC = 0.249       !Fract. Blood Flow to Poorly Perfused T.
```

```
QRC = 1.0 - QLC - QFC - QBC - QSC - QGC  !Fract.
Blood Flow to Richly Perfused T.


CONSTANT      BW = 0.350       !Body Weight(kg)
CONSTANT      VLC = 0.026      !Volume Fraction Liver
CONSTANT      VFC = 0.2142     !Volume Fraction Fat
CONSTANT      VBC = 0.020      !Volume Fraction Brain
CONSTANT      VGC = 0.0249     !Volume Fraction GI Tract
CONSTANT      VSC = 0.4371      !Volume Fraction Poorly Perfused T.
CONSTANT      VNC = 0.0076     !Volume Fraction Lung
CONSTANT      VVBC = 0.0592 !Volume Fraction Venous Blood
CONSTANT      VABC = 0.0198 !Volume Fraction Arterial Blood

VRC = 1.0 - VLC - VFC - VBC - VSC - VNC - VVBC - VABC - VGC   !Volume
Fraction Richly Perfused T.

!***** Chemical Specific Parameters for TOL *****

!Partition Coefficients from Thrall et al., 2002
CONSTANT      PL = 2.01        !Liver/Blood Partition Coefficient
CONSTANT      PF = 86.19       !Fat/Blood Partition Coefficient
CONSTANT      PBR = 1.72       !Brain/Blood Partition Coefficient
CONSTANT      PG = 2.62        !GI/Blood Partition Coefficient
CONSTANT      PS = 1.32        !Poorly/Blood Partition Coefficient
CONSTANT      PR = 3.04        !Richly/Blood Partition Coefficient
CONSTANT      PB = 21.0        !Blood/Air Partition Coefficient
CONSTANT      PN = 1.14        !Lung/Blood Partition Coefficient
CONSTANT      MW = 92.14       !Molecular Wt (g/mol)

!***** Metabolism Parameters - VMAX/KM from Pierce et al., 1996
CONSTANT      VMAXC = 4.8      !Max Rate TOL metabolism (mg/hr-kg)
CONSTANT      KM = 0.55        !Affinity Constant for TOL (mg/l)

!***** Dosing & Exposure Variables *****

CONSTANT   CONC = 250.   !Inhalation Concentration (ppm)

!***** Timing Commands *****

SCHEDULE DS1 .AT. TCHNG       !Use discrete at discontinuities
```

```
CIZONE = 1.0                    !Start with inhalation on

CONSTANT TSTOP = 8.             !Length of experiment (hrs)
CONSTANT TCHNG = 2.             !Length of inhalation exposure

CONSTANT POINTS = 100.          !Number of points in plot
CINT = TSTOP/POINTS             !Communication interval

!***** Inhalation Exposure Definition *****

AIO = (CONC * MW)/24450         !Initial Chamber Conc (mg/l)

!***** Oral Exposure Definition *****

CONSTANT      DV = 0.002        !Dosing Volume in L/kg
CONSTANT       SOCO = 100000 !Dosing Soln Conc, mg/L
CONSTANT      KA = 5.0          !First Order GI abs, 1/hr

ODTOL = DV*BW*SOCO              !Bolus gavage dose in mg
ORTOL = (DV*SOCO*BW)/BW         !Bolus dose in mg/kg

!***** Scaled Parameters *****

QC = QCC * (BW**0.74) !Cardiac Output (l/hr)
QP = QPC * (BW**0.74)    !Alveolar Ventilation Rate (l/hr)
QL = QLC * QC            !Flow Liver Compartment (l/hr)
QF = QFC * QC            !Flow Fat Compartment (l/hr)
QB = QBC * QC            !Flow Brain Compartment (l/hr)
QG = QGC * QC            !Flow GI Compartment (l/hr)
QS = QSC * QC            !Flow Slowly Perf. Tis. Cmpt. (l/hr)
QR = QRC * QC            !Flow Richly Perf. Tis. Cmpt. (l/hr)
VL = VLC * BW            !Volume Liver Compartment, Total
VF = VFC * BW            !Volume Fat Compartment
VB = VBC * BW            !Volume Brain Compartment
VG = VGC * BW            !Volume GI Compartment
VS = VSC * BW            !Volume Slowly Perfused Tis. Cmpt.
VR = VRC * BW            !Volume Richly Perfused Tis. Cmpt.
VMAX= VMAXC * BW**0.74      !VMAX scaled

VVB = VVBC * BW          !Volume Venous Blood Cmpt. VAB
= VABC * BW     !Volume Arterial Blood Cmpt.
VN = VNC * BW            !Volume Lung Cmpt.
```

```
END      !**** END OF INITIAL ****

DYNAMIC        !Code executed at end of each commun. interval

ALGORITHM      IALG = 2          !Gear Method for Stiff Systems (LSODE)

DISCRETE DS1             !Discontinuity in Simulation executed
                         !when inhalation exposure ends
CIZONE = 0.0             !Turn inhalation off
CALL LOGD(.TRUE.)        !Forced logging for plots
END

DERIVATIVE

!Gavage oral dose of Toluene in mg
RDSTOM = -KA*STOMD
STOMD = INTEG(RDSTOM, ODTOL)

!CI - Concentration TOL in inhaled air (mg/l)
RAI = QP * C             !Rate TOL to lung (mg/hr)
AI = INTEG (RAI, 0.)     !Amount TOL entering lung, mg
CI = AIO * CIZONE

!CA - Concentration TOL in arterial blood (mg/l)
! CA1 - Concentration part to lung
!AAB - Amount TOL in arterial blood (mg)
RAAB = QC * CA1 - QC * CA
AAB = INTEG(RAAB, 0.)
CA = AAB/VAB

!AX - Amount TOL exhaled (mg)
RAX = QP * CX            !Rate TOL exhaled (mg/hr)
AX = INTEG (RAX, 0.)
CX = CA1/PB              !Conc. TOL in exhaled air(mg/l)
CXPPM = ((0.7 * CX) + (0.3 * CI)) * (24450/MW) !ppm
AXKG = AX/BW             !mg exhaled/kg body weight

!AN - Amount TOL in lung (mg)
RAN = QC * CV + QP * CI - QC * CA1 - QP * CX
AN = INTEG (RAN, 0.)
```

```
CA1 = AN/(VN * PN)
CN = AN/VN

!AS - Amount TOL in slowly perfused tissues (mg)
RAS = QS * (CA - CVS)     !Rate of change in conc. (mg/hr)
AS = INTEG (RAS, 0.)
CVS = AS / (VS * PS)      !Conc partition to slow per. tis.(mgl)
CS = AS / VS              !Conc in volume slow per. tis.(mg/l)

!AR - Amount TOL in rapidly perfused tissues (mg)
RAR = QR * (CA - CVR) !Rate of change in conc. (mg/hr)
AR = INTEG (RAR, 0.)
CVR = AR / (VR * PR)      !Conc partition to rap per. tis.(mg/l)
CR = AR / VR              !Conc in volume rap per. tis.(mg/l)

!ABR - Amount TOL in brain (mg)
RABR = QB * (CA - CVBR)          !Rate of change in conc (mg/hr)
ABR = INTEG (RABR, 0.)
CVBR = ABR / (VB * PBR)          !Conc partition to brain(mg/l)
CBR = ABR / VB                   !Conc in volume brain(mg/l)
AUCBR = INTEG(CBR, 0.)           !AUC for TOL in brain

!AF - Amount TOL in fat tissue(mg)
RAF = QF * (CA - CVF)     !Rate of change in conc(mg/hr)
AF = INTEG (RAF, 0.)
CVF = AF / (VF * PF)      !Conc partition to fat(mg/l)
CF = AF / VF              !Conc in fat volume(mg/l)    !AG - Amount TOL in gut
tissue(mg)
!RAG - rate of change TOL in gut conc, mg/hr
RAG = QG * (CA - CVG) - RDSTOM
AG = INTEG (RAG, 0.)
CVG = AG / (VG * PG)      !Conc partition to gut (mg/l)
CG = AG / VG              !Conc in gut volume(mg/l)

!AL - Amount TOL in liver(mg)
!RAL - rate of change in liver conc, mg/hr
RAL = (QL * CA) + (QG * CVG) - ((QL+QG) * CVL) - RAM
AL = INTEG (RAL, 0.)
CVL = AL / (VL * PL)      !Conc partition to liver(mg/l)
CL = AL / VL              !Conc in liver volume(mg/l)

!AUCPO - Amount TOL oxidatively metabolized (mg)
```

```
!RAM - Rate of oxidative metabolism of TOL (mg/hr)
RAM = (VMAX * CVL) / (KM + CVL)
AUCPO = INTEG (RAM, 0.)
AUCKG = AUCPO / BW !Amount TOL metabolized/kg body weight

!CV - TOL mixed venous blood concentration (mg/l)
!RAVB - Rate of change in concentration (mg/hr)
RAVB = (QL+QG)*CVL) + QF*CVF + QS*CVS + QR*CVR + QB*CVBR - QC * CV
AVB = INTEG(RAVB, 0.)
CV = AVB/VVB              !Conc in venous blood volume (mg/l)
AUCV = INTEG(CV,0.)       !AUC for toluene in venous blood

!PMASS - TOL Mass balance(mg)
PMASS = AN + AF + AG + AL + AS + AR + ABR + AUCPO + AX + AVB +
          AAB + STOMD

TERMT (T .GE. TSTOP)     !terminate solution

END       !END OF DERIVATIVE

!**Code to calculate variables used in checking mass balance**

BALPC = (AI + ODTOL) - PMASS
TBALPC = ABS(BALPC)

END       !END OF DYNAMIC

END       !END OF PROGRAM
```

APPENDIX D

TOLUENE SIMULATIONS

Vernon Benignus, Elaina M. Kenyon, William Boyes, and Philip Bushnell
2/22/2013

Acute exposure to toluene vapor impairs neurologic function. The degrees of neurologic impairment produced by exposures to toluene, and dose responserelationships, have been determined using a variety of behavioral procedures. Some of these behavioral procedures, such as choice reaction time tasks, have also been used to evaluate the acute consequences of exposure to another common intoxicant, ethanol. This circumstance allows the potency of toluene and ethanol to be

compared relative to a common degree of behavioral impairment. Because the behavioral impairments caused by ethanol intoxication have also been associated with fatal automobile accidents in a dose-effect manner, it is possible to estimate the degree of toluene exposure associated with a level of impairment that might increase the probability of causing a fatal automobile accident if an exposed person were also driving at the same time. In addition to the probability of an automobile accident, this level of impairment would also be expected to put a person who was not driving at risk for other accidents or dangers given their unique circumstances and surroundings. With this approach, it is possible to estimate the potential severity of acute behavioral impairments caused by toluene in terms that are relevant for AEGL value determinations.

Behavioral Consequences of Toluene Exposure

Simulations comparing the behavioral effects of toluene and ethanol were made to provide context for the danger of toluene exposure in terms of the danger associated with comparable levels of intoxication with ethanol. These simulations used a behavioral effect (speed of choice reaction time) as a dependent variable. In these tests, the subject must make a decision about which response is correct as quickly as possible. Table D-1 and Figure D-1 show the severity of a decrement in reaction time (percent of maximum possible effect) as a function of brain toluene concentration, and also the blood ethanol concentrations equivalent to these brain toluene concentrations. Brain toluene concentrations are related quantitatively to blood ethanol concentrations in terms of the magnitude of change in reaction time associated with each chemical (Benignus et al. 2005).

In addition, Table D-1 and Figure D-1 show corresponding increases in fatal automobile crashes as a function of degree of intoxication with either toluene or ethanol. These functions were derived from data relating the increased risk of a fatal car crash to blood ethanol concentration and the quantitative relationship between the effects of toluene and ethanol on reaction time. These relationships allow one to estimate the number of fatal automobile accidents that would be produced by toluene exposure as a function of the degree of intoxication (Benignus et al. 2011). It should be noted that the increase in fatal automobile accidents is given as the number of fatalities per 1,000 drivers who had the toxicant in their bodies while driving.

From Table D-1 it may be concluded that a concentration of toluene in brain of 119 µM produces a degree of intoxication associated with about 13% reduction in speed of choice reaction time. This degree of impairment is also associated with 0.08 g/dl of venous ethanol, a concentration that defines legal intoxication and is associated with an increase over baseline of 305 fatal automobile accidents per 1,000 drivers. Almost half of drivers with 0.10 g/dl venous ethanol or a brain toluene concentration of 241 µM would be expected to have fatal automobile accidents.

Inhaled Concentrations of Toluene Required to Produce Specific Brain Concentrations

In addition to the duration of exposure, alveolar ventilation, which depends upon physical activity, affects the concentration of toluene in the inhaled air that is required to produce a given brain toluene concentration. Table D-2 and Figure D-2 give approximate concentrations of toluene in inhaled air for a person exercising at four levels of exertion for two brain concentrations and for five exposure durations of interest. This illustrates the large impact of exertion on toluene uptake.

TABLE D-1 The Importance of the Behavioral Effects of Toluene Exposure Estimated via the Alcohol Effects on Fatal Automobile Accidents and Employing the Equivalent Dose of Brain Toluene

Venous Blood Alcohol (g/dL)	Proportion of Fatal Automobile Accidents Greater Than Baseline[a]	Equivalent Brain Toluene (μM)[b]	Effect on Choice Reaction Time Test (% of Maximum)[c]
0.10	0.478	241.0	26.2
0.09	0.386	172.0	19.1
0.08	0.305	119.0	13.1
0.07	0.216	83.1	8.9
0.06	0.132	48.8	4.9

[a] Fatal automobile accident estimates were obtained from Zador (1991) and Zador et al. (2000) as expressed in Figure 2 of Benignus et al. (2011). The proportion of persons who were killed in a single-car crash with a measured post-mortem blood-ethanol concentration, relative to persons driving with that same blood-ethanol concentration who did not crash, is expressed as a proportional increment above baseline (0.00 g/dL). [b] Toluene/alcohol equivalence was computed using Equation 2 in Benignus et al. (2011).
[c] Behavioral effect magnitudes were computed using Equation 1, with human parameters for the low motivation case, from Table 4 of Benignus et al. (2009).

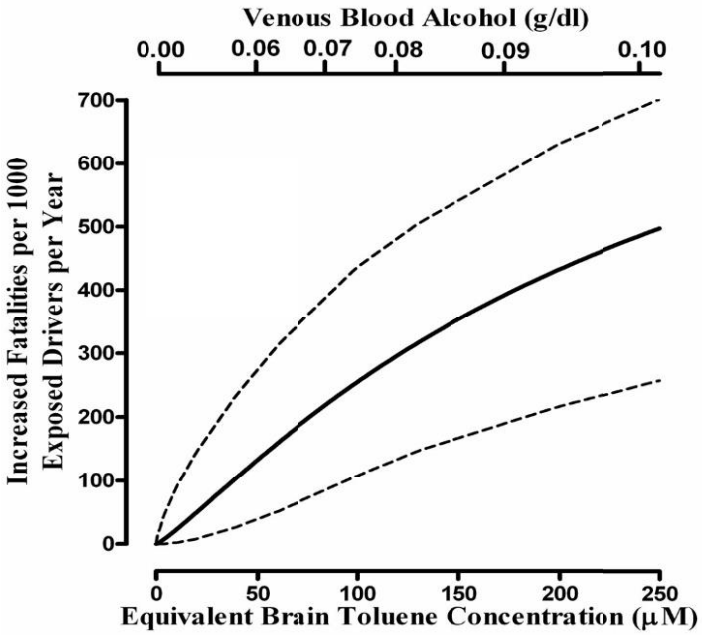

FIGURE D-1 The effect of alcohol intoxication (top horizontal axis) on fatal automobile accidents (per 1,000 drivers per year) compared with the equivalent amount of toluene in the brain (μM). This graph is a modified form of Figure 3 in Benignus et al. (2011). The alcohol axis was constructed from Figrure 1c from the same source. The plotted functions reflect the mean estimate (solid line) and the upper and lower 95% confidence limits (dashed lines).

TABLE D-2 Approximate Exposures Required to Produce Brain Toluene Concentrations Given in Table D-1 as Determined by the GPAT Model

	Concentration Required for 241 μM Brain Toluene (ppm)				Concentration Required for 119 μM Brain Toluene (ppm)			
Time	Lying	Standing	1 mph	2 mph	Lying	Standing	1 mph	2 mph

10 min	2,290	1,860	1,350	1,000	1,150	930	670	500
30 min	1,320	1,000	680	480	700	520	350	240
1 h	1,010	730	460	320	540	390	240	165
4 h	555	390	250	200	325	230	140	110
8 h	445	320	220	190	275	190	130	100

The values in the table were approximated by iteratively applying GPAT (Benignus et al. 2006). The modeled subject was lying down, standing, or walking at 1 or 2 mph.

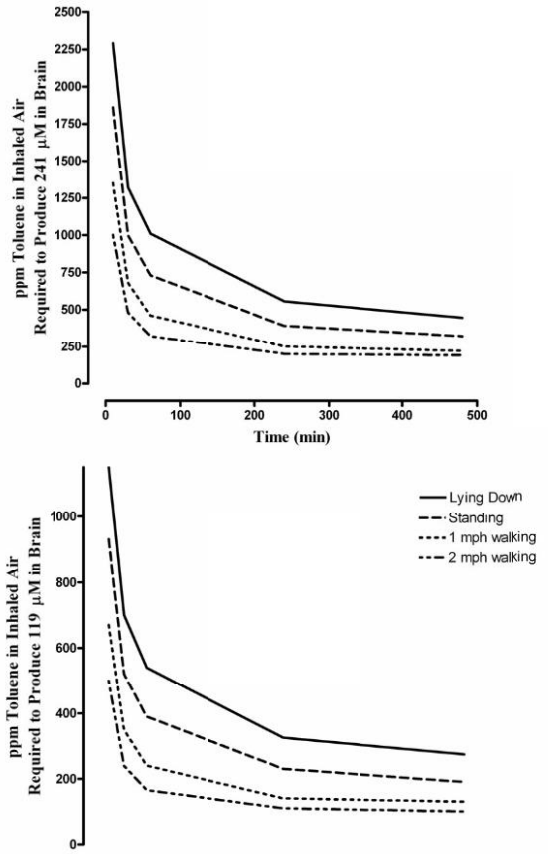

FIGURE D-2 Concentration of inhaled toluene (ppm) required to produce brain toluene concentrations of 241 or 119 µM at four exercise levels. The two brain toluene concentrations are equivalent to venous concentrations of alcohol of 0.1 or 0.08 g/dl. Those

concentrations are roughly approximate values of ppm generated by the GPAT model (Benignus et al. 2006).

Inhaled Air Concentrations Required to Produce Toluene Concentrations of 119 or 241 µM in the Brain

All calculations so far were made using the GPAT model, because the Dennison model does not have a brain compartment. In order to make exposure estimates with the accepted Dennison model, (a) a GPAT model was used to estimate the venous concentrations of toluene required to produce brain concentrations of 110 or 241 µM and (b) the Dennison model was used to determine the ppm values necessary to produce these venous concentrations. These venous and inhaled-air concentrations are presented in Table D-3.

TABLE D-3 Inhaled Air and Venous Concentrations of Toluene Required to Produce Either 119 or 241 µM Brain Toluene Concentrations Computed from the Dennison PBPK Model

Time	For 119 µM		For 241 µM	
	Air (ppm)	Venous (mg/L)		
10 min	625	2.07	1,498	5.24
30 min	372	2.75	729	5.87
1 h	312	3.05	597	6.49
4 h	258	3.55	481	7.52
8 h	239	3.66	436	7.73

Behavioral Contingencies

For both rats and humans, sensitivity to a given concentration of a solvent in the brain depends upon the situation under which the exposed individual was tested (Benignus et al. 2007, 2009). When a behavioral decrement has little consequence to the subject, the behavioral disruption by the toxicant will be maximal. If the subject loses a reward for poor performance, the effect of the tested toxicant will be reduced, or more toxicant will be necessary to disrupt the behavior. If painful punishment follows poor performance, the effect of the tested toxicant is greatly reduced. For example, rats working to avoid painful shocks are less susceptible to toluene exposure than are rats working for a food reward. Rats working for a food reward are less susceptible than are some nonmotivated neurophysiologic procedures that are not subject to either reward or punishment. It is important to consider behavioral measurements that are reasonably comparable if sensitivity is to be compared across factors such as different behavioral tasks or across different species.

Quantitative Rat-to-Human Extrapolation

Using ED_{10} values for various situations in rats and humans from Figure 3 in Benignus et al. (2009), a table of extrapolation ratios was created (see Table D-4). Table D-4 shows that if experimental procedures are the same in rats and humans, the same brain solvent concentrations in the two species should produce the same ED_{10}. In contrast, if the contingencies on performance differ, then ED_{10}s will differ accordingly. Thus, modeling studies with rats suggest that the ED_{10} of a subject whose behavior is minimally constrained by contingencies will be lower by a factor of 86 compared to a subject avoiding punishment (Benignus et al. 2009). Thus quantitative rat-human extrapolation requires information about the experimental contingencies applied during the tests; data from animal studies suggest that if the contingencies differ, then the extrapolation must take into account their relative impacts of the behavioral contingencies applied to each species.

Acute Exposure Guideline Levels

TABLE D-4 Extrapolating Factors[a] from Rats to Humans Depending on Experimental Conditions

	None	Minimum	Withhold reward	Painful punishment
None	1.00	7.30	19.40	86.30
Minimum	–	1.00	2.70	11.80
Withhold Reward	–	–	1.00	4.40
Painful punishment	–	–	–	1.00

[a] Divide rat ED_{10} for the appropriate rat experimental condition by the extrapolation factor to calculate the human ED_{10}. Factors calculated from the data to produce Figure 3 in Benignus et al. (2009).

REFERENCES

Benignus, V.A., P.J. Bushnell, and W.K. Boyes. 2005. Toward cost-benefit analysis of acute behavioral effects of toluene in humans. Risk Anal 25(2):447-456.

Benignus, V.A., T. Coleman, C.R. Eklund, and E.M. Kenyon. 2006. A general physiological and toxicokinetic (GPAT) model for simulating complex toluene exposure scenarios in humans. Toxicol. Mech. Methods 16(1):27-36.

Benignus, V.A., W.K. Boyes, E.M. Kenyon, and P.J. Bushnell. 2007. Quantitative comparison of the acute neurotoxicity of toluene in rats and humans. Toxicol. Sci. 100(1):146-155.

Benignus, V.A., P.J. Bushnell, W.K. Boyes, C. Eklund, and E.M. Kenyon. 2009. Neurobehavioral effects of acute exposure to four solvents: Meta-analyses. Toxicol. Sci. 109(2):296-305.

Benignus, V.A., P.J. Bushnell, and W.K. Boyes. 2011. Estimated rate of fatal automobile accidents attributable to acute solvent exposure at low inhaled concentrations. Risk Anal. 31(12):1935-1948.

Zador, P.L. 1991. Alcohol-related relative risk of fatal driver injuries in relation to driver age and sex. J. Stud. Alcohol 52(4):302-310.

Zador, P.L., S.A. Krawchuck, and R.B. Voas. 2000. Alcohol-related relative risk of driver fatalities and driver involvement in fatal crashes in relation to driver age and gender: An update using 1996 data. J. Stud. Alcohol 61(3):387-395.

APPENDIX E

ACUTE EXPOSURE GUIDELINE LEVELS FOR TOLUENE

AEGL-1 VALUES

10 min	30 min	1 h	4 h	8 h
67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)	67 ppm (250 mg/m^3)

Key references: Multiple clinical studies, including:

(1) Astrand, I., H. Ehrner-Samuel, A. Kilbom, and P. Ovrum. 1972. Toluene exposure. I. Concentration in alveolar air and blood at rest and during exercise. Scand. Work Environ. Health 9:119-130.

(2) Gamberale, F., and M. Hultengren. 1972. Toluene exposure. II. Psychophysiological functions. Work Environ. Health. 9(3):131-139.

(3) Baelum, J., G.R. Lundqvist, L. Molhave, and N.T. Andersen. 1990. Human response to varying concentrations of toluene. Int. Arch. Occup. Environ. Health 62(1):65-72. Test species/Strain/Number: Humans, (1) 15, both sexes; (2) 12 males; (3) 71 subjects

Exposure route/Concentrations/Durations: Inhalation; (1) 100 or 200 ppm for 60 min, exercise incorporated into protocol; (2) 100, 300, 500, or 700 ppm, successive 20-min exposures for a total of 85 min (one 5-min break), exposure via a mouthpiece; (3) 100 ppm for 7.5 h, varying exposures of 50-300 ppm (TWA of 100 ppm) for 7.5 h.

Effects:

(1) 100 or 200 ppm with exercise: no effect on heart rate, pulmonary ventilation, oxygen consumption, or blood lactate; subjective symptoms not assessed.

(2) One of 12 subjects able to distinguish between control and toluene exposure
100 ppm: no effect on reaction time
300 ppm: increase in simple reaction time
500 ppm: increase in complex reaction time
700 ppm: decrease in perceptual speed at end of exposure

(3) 100 ppm: no ocular irritation, complaints of "poor air quality," irritation of nose and lower airways.
50-300 ppm (TWA of 100 ppm): same symptoms as above.

End point/Concentration/Rationale: Weight of evidence from multiple clinical studies indicated that toluene at 200 ppm for up to 8 h would be without effects that exceed the definition of AEGL-1. Slight irritation reported in some studies, but not others.

Uncertainty factors/Rationale:
Intraspecies: 3, the minimum alveolar concentration for volatile anesthetics differs by no more than 2- to 3-fold in the human population.

Modifying factor: None

Animal-to-human dosimetric adjustment: None

Time scaling: Not applied; steady-state at 67 ppm is approached fairly rapidly.

Data adequacy: Twenty clinical studies, many of them recent and well-conducted, addressed sensory irritation and the threshold for CNS effects. Metabolism and monitoring studies also indicate a lack of substantial effects at 200 ppm.

Acute Exposure Guideline Levels

AEGL-2 VALUES

10 min	30 min	1 h	4 h	8 h
1,400 ppm[a] (5,300 mg/m^3)	760 ppm (2,900 mg/m^3)	560 ppm (2,100 mg/m^3)	310 ppm (1,200 mg/m^3)	250 ppm (940 mg/m^3)

Reference: Bushnell, P.J., W.M. Ohiro, T.E. Samsam, V.A. Benignus, Q.T. Krantz, and E.M. Kenyon. 2007a. A Dosimetric analysis of the acute behavioral effects of inhaled toluene in rats. Toxicol. Sci. 99(1):181-189.

Test species/Strain/Number: Rat; Long-Evans; 16 male rats exposed in groups of 4.

Exposure route/Concentrations/Durations: Inhalation; 0, 1,200, 1,600, 2,000, or 2,400 ppm for up to 70 min.

Effects: Reaction time doubled compared with air-exposed controls. Concentrationrelated increase in reaction time. NOAEL for a doubling of reaction time was 1,600 ppm for a 34-min exposure.

End point/Concentration/Rationale: Doubling of reaction time, threshold of 1,600 ppm for 34-min exposure

Uncertainty factors/Rationale:
Interspecies: 1, PBPK modeling eliminated the toxicokinetic component of the uncertainty factor; the pharmacodynamic component was assigned a factor of 1 because similar central-nervous-system effects were observed in rodents and humans.
Intraspecies: 3, the minimum alveolar concentration for volatile anesthetics differs by no more than 2- to 3-fold in the human population.

Modifying factor: None

Animal-to-human dosimetric adjustment: PBPK modeling performed

Time scaling: PBPK modeling was used to determine the equivalent exposure concentrations that yield the dose metric at each of the AEGL exposure durations.

Data adequacy: The values are supported by a comparison of the AEGL values and corresponding effect levels from ethanol consumption in humans (Benignus et al. 2011).

[a] Concentration is one-tenth or more of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, safety considerations against the hazard of explosion must be taken into account.

AEGL-3 VALUES

10 min	30 min	1 h	4 h	8 h
–[a]	5,200 ppm[b] (20,000 mg/m^3)	3,700 ppm[b] (14,000 mg/m^3)	1,800 ppm[b] (6,800 mg/m^3)	1,400 ppm[b] (5,300 mg/m^3)

Reference: Mullin, L.S., and N.D. Krivanek. 1982. Comparison of unconditioned reflex and conditioned avoidance tests in rats exposure by inhalation to carbon monoxide, 1,1,1trichloroethane, toluene or ethanol. Neurotoxicity 3(1):126-137.

Test species/Strain/Number: Rats, CD, 6 males per group

Exposure route/Concentrations/Durations: Inhalation, 810, 1,660, or 3,100 ppm for 4 h; 6,250 ppm for 2 h

Effects: No deaths after a 2-h exposure at 6,250 ppm

End point/Concentration/Rationale: NOAEL for lethality, 6,250 ppm for 2 h

Uncertainty factors/Rationale:
Interspecies: 1, PBPK modeling eliminated the toxicokinetic component of the uncertainty factor; the pharmacodynamic component was assigned a factor of 1 because similar central-nervous-system effects were observed in rodents and humans.
Intraspecies: 3, the minimum alveolar concentration for volatile anesthetics differs by no more than 2- to 3-fold in the human population.

Modifying factor: None

Animal-to-human dosimetric adjustment: PBPK modeling performed

Time scaling: PBPK modeling was used to determine the equivalent exposure concentrations that yield the dose metric at each of the AEGL exposure durations.

Data adequacy: There are multiple lethality studies in rats and mice. The AEGL-3 values are supported by the 20-min NOAEL of 12,000 ppm for lethality in the mouse (Bruckner and Peterson 1981a), the 2-h NOAEL of 5,000 ppm for lethality in rats (Kojima and Kobayashi 1973), the 4-h NOAEL of 6,000 ppm for lethality in rats (Wada et al. 1989), the NOAEL of 6,000 ppm in mice repeatedly exposed for 30 min/day (Moser and Balster 1981), and the chronic NOAEL of 1,200 ppm for mice and rats (NTP 1990).

[a] The 10-min AEGL-3 value of 10,000 ppm (38,000 mg/m^3) is higher than 50% of the

lower explosive limit of 14,000 ppm for toluene in air. Therefore, extreme safety considerations against the hazard of explosion must be taken into account. *b* Concentration is one-tenth or more of the lower explosive limit of 14,000 ppm for toluene in air. Therefore, safety considerations against the hazard of explosion must be taken into account.