

**TOXICOLOGICAL PROFILE FOR
2-BUTOXYETHANOL AND 2-BUTOXYETHANOL ACETATE**

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry**

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UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

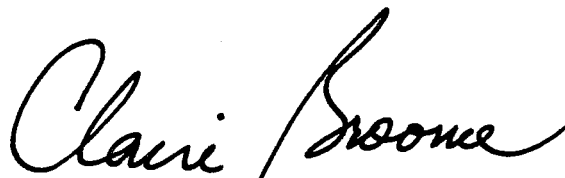
The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Claire V. Broome, M.D.
Acting Administrator
Agency for Toxic Substances and
Disease Registry

***Legislative Background**

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). Section 211 of SARA also amended Title 10 of the U. S. Code, creating the Defense Environmental Restoration Program. Section 2704(a) of Title 10 of the U. S. Code directs the Secretary of Defense to notify the Secretary of Health and Human Services of not less than 25 of the most commonly found unregulated hazardous substances at defense facilities. Section 2704(b) of Title 10 of the U. S. Code directs the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare a toxicological profile for each substance on the list provided by the Secretary of Defense under subsection (b).

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS(S):

Olivia Harris, M.A.
ATSDR, Division of Toxicology, Atlanta, GA

Sharon Wilbur, M.S.
Research Triangle Institute, Research Triangle Park, NC

Julia George, Ph.D.
Research Triangle Institute, Research Triangle Park, NC

Carol Eisenmann, Ph.D.
Sciences International, Inc., Alexandria, VA

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures consistency with ATSDR policy.
2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.
3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
4. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for 2-butoxyethanol and 2-butoxyethanol acetate. The panel consisted of the following members:

1. Dr. Walter Decker, Private Consultant, 3223 Malapai Lane, El Paso, Texas 79904
2. Dr. Arthur Gregory, Private Consultant, 220 West Ash Road, Sterling, Virginia 20164
3. Dr. Robert Rubin, Professor, Department of Environmental Health Sciences, Johns Hopkins School of Public Health, 615 North Wolfe Street, Baltimore, MD 21205
4. Dr. Martin Alexander, Professor, Cornell University, Ithaca, NY 14853
5. Dr. Carson Canaway, Research Scientist, Mahopac, NY 10541
6. Dr. Samuel Kacew, Professor, Department of Pharmacology, University of Ottawa, Ottawa, Ontario, Canada K1H 8M5

These experts collectively have knowledge of 2-butoxyethanol and 2-butoxyethanol acetate's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

CONTENTS

FOREWORD	v
CONTRIBUTORS	vii
PEER REVIEW	ix
LIST OF FIGURES	xv
LIST OF TABLES	xvii
1. PUBLIC HEALTH STATEMENT	1
1.1 WHAT ARE 2-BUTOXYETHANOL AND 2-BUTOXYETHANOL ACETATE?	1
1.2 WHAT HAPPENS TO 2-BUTOXYETHANOL OR 2-BUTOXYETHANOL ACETATE WHEN THEY ENTER THE ENVIRONMENT?	3
1.3 HOW MIGHT I BE EXPOSED TO 2-BUTOXYETHANOL OR 2-BUTOXYETHANOL ACETATE?	4
1.4 HOW CAN 2-BUTOXYETHANOL AND 2-BUTOXYETHANOL ACETATE ENTER AND LEAVE MY BODY?	5
1.5 HOW CAN 2-BUTOXYETHANOL OR 2-BUTOXYETHANOL ACETATE AFFECT MY HEALTH?	6
1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 2-BUTOXYETHANOL OR 2-BUTOXYETHANOL ACETATE?	9
1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?	9
1.8 WHERE CAN I GET MORE INFORMATION?	10
2. HEALTH EFFECTS	13
2.1 INTRODUCTION	13
2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE	13
2.2.1 Inhalation Exposure	15
2.2.1.1 Death	15
2.2.1.2 Systemic Effects	39
2.2.1.3 Immunological and Lymphoreticular Effects	52
2.2.1.4 Neurological Effects	53
2.2.1.5 Reproductive Effects	54
2.2.1.6 Developmental Effects	55
2.2.1.7 Genotoxic Effects	56
2.2.1.8 Cancer	56
2.2.2 Oral Exposure	56
2.2.2.1 Death	57
2.2.2.2 Systemic Effects	59
2.2.2.3 Immunological and Lymphoreticular Effects	114
2.2.2.4 Neurological Effects	117
2.2.2.5 Reproductive Effects	119
2.2.2.6 Developmental Effects	121

2.2.2.7	Genotoxic Effects	122
2.2.2.8	Cancer	123
2.2.3	Dermal Exposure	123
2.2.3.1	Death	123
2.2.3.2	Systemic Effects	125
2.2.3.3	Immunological and Lymphoreticular Effects	147
2.2.3.4	Neurological Effects	148
2.2.3.5	Reproductive Effects	149
2.2.3.6	Developmental Effects	150
2.2.3.7	Genotoxic Effects	150
2.2.3.8	Cancer	150
2.3	TOXICOKINETICS	151
2.3.1	Absorption	151
2.3.1.1	Inhalation Exposure	151
2.3.1.2	Oral Exposure	154
2.3.1.3	Dermal Exposure	155
2.3.2	Distribution	160
2.3.2.1	Inhalation Exposure	160
2.3.2.2	Oral Exposure	162
2.3.2.3	Dermal Exposure	163
2.3.2.4	Other Routes of Exposure	163
2.3.3	Metabolism	164
2.3.4	Elimination and Excretion	173
2.3.4.1	Inhalation Exposure	173
2.3.4.2	Oral Exposure	177
2.3.4.3	Dermal Exposure	179
2.3.5	Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	181
2.3.5.1	Summary of PBPK Models	182
2.3.5.2	2-Butoxyethanol PBPK Model Comparison	184
2.3.5.3	Discussion of Models	184
2.4	MECHANISMS OF ACTION	204
2.4.1	Pharmacokinetic Mechanisms	204
2.4.2	Mechanisms of Toxicity	205
2.4.3	Animal-to-Human Extrapolations	211
2.5	RELEVANCE TO PUBLIC HEALTH	212
2.6	BIOMARKERS OF EXPOSURE AND EFFECT	251
2.6.1	Biomarkers Used to Identify or Quantify Exposure to 2-Butoxyethanol	252
2.6.2	Biomarkers Used to Characterize Effects Caused by 2-Butoxyethanol	253
2.7	INTERACTIONS WITH OTHER CHEMICALS	254
2.8	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	255
2.9	METHODS FOR REDUCING TOXIC EFFECTS	256
2.9.1	Reducing Peak Absorption Following Exposure	256
2.9.2	Reducing Body Burden	257
2.9.3	Interfering with the Mechanism of Action for Toxic Effects	257
2.10	ADEQUACY OF THE DATABASE	258
2.10.1	Existing Information on Health Effects of 2-Butoxyethanol	259
2.10.2	Identification of Data Needs	262
2.10.3	Ongoing Studies	277

3. CHEMICAL AND PHYSICAL INFORMATION	279
3.1 CHEMICAL IDENTITY	279
3.2 PHYSICAL AND CHEMICAL PROPERTIES	279
4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL	287
4.1 PRODUCTION	287
4.2 IMPORT/EXPORT	288
4.3 USE	288
4.4 DISPOSAL	290
5. POTENTIAL FOR HUMAN EXPOSURE	291
5.1 OVERVIEW	291
5.2 RELEASES TO THE ENVIRONMENT	295
5.2.1 Air	295
5.2.2 Water	296
5.2.3 Soil	297
5.3 ENVIRONMENTAL FATE	297
5.3.1 Transport and Partitioning	297
5.3.2 Transformation and Degradation	299
5.3.2.1 Air	299
5.3.2.2 Water	300
5.3.2.3 Sediment and Soil	301
5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT	301
5.4.1 Air	301
5.4.2 Water	302
5.4.3 Sediment and Soil	303
5.4.4 Other Environmental Media	303
5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE	304
5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	313
5.7 ADEQUACY OF THE DATABASE	313
5.7.1 Identification of Data Needs	314
5.7.2 Ongoing Studies	318
6. ANALYTICAL METHODS	319
6.1 BIOLOGICAL SAMPLES	319
6.2 ENVIRONMENTAL SAMPLES	323
6.3 ADEQUACY OF THE DATABASE	325
6.3.1 Identification of Data Needs	325
6.3.2 Ongoing Studies	326
7. REGULATIONS AND ADVISORIES	327
8. REFERENCES	333
9. GLOSSARY	355

APPENDICES

A. MINIMAL RISK LEVEL (MRL) WORKSHEETS A-1

B. USER'S GUIDE B-1

C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS C-1

LIST OF FIGURES

2-1	Levels of Significant Exposure to 2-Butoxyethanol—Inhalation	32
2-2	Levels of Significant Exposure to 2-Butoxyethanol Acetate—Inhalation	36
2-3	Levels of Significant Exposure to 2-Butoxyethanol—Oral	90
2-4	Levels of Significant Exposure to 2-Butoxyethanol Acetate—Oral	96
2-5	Levels of Significant Exposure to 2-Butoxyacetic Acid—Oral	97
2-6	Scheme for metabolism of 2-Butoxyethanol	165
2-7	Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance	183
2-8	Schematic Drawing of PBPK Model for Simulation of 2-Butoxyethanol Toxicokinetics	185
2-9	PBPK Model for 2-Butoxyethanol Disposition in Rats	186
2-10	Model of Metabolic Pathway of 2-Butoxyethanol	187
2-11	PBPK Model of 2-Butoxyethanol and 2-Butoxyacetic Acid	188
2-12	Existing Information on Health Effects of 2-Butoxyethanol	260
2-13	Existing Information on Health Effects of Butoxyethanol Acetate	261
5-1	Frequency of NPL Sites With 2-Butoxyethanol Contamination	292

LIST OF TABLES

2-1	Levels of Significant Exposure to 2-Butoxyethanol—Inhalation	17
2-2	Levels of Significant Exposure to 2-Butoxyethanol Acetate—Inhalation	27
2-3	Levels of Significant Exposure to 2-Butoxyethanol—Oral	60
2-4	Levels of Significant Exposure to 2-Butoxyethanol Acetate—Oral	88
2-5	Levels of Significant Exposure to 2-Butoxyacetic Acid—Oral	89
2-6	Levels of Significant Exposure to 2-Butoxyethanol—Dermal	126
2-7	Levels of Significant Exposure to 2-Butoxyethanol Acetate—Dermal	136
2-8	Metabolism of 2-Butoxyethanol by Human and Rat Hepatocytes	172
2-9	Parameters Used in the Johanson PBPK Model	191
2-10	Parameters Used in the Shyr PBPK Model	194
2-11	Parameters Used in the Physiologically Based Pharmacokinetic Model for 2-Butoxyethanol and 2-Butoxyacetic Acid	198
2-12	Human Physiological Parameters Adjusted for Light-Moderate Exercise	201
2-13	Genotoxicity of 2-Butoxyethanol <i>In Vitro</i>	250
3-1	Chemical Identity of 2-Butoxyethanol	280
3-2	Chemical identity of 2-Butoxyethanol Acetate	281
3-3	Physical and Chemical Properties of 2-Butoxyethanol	282
3-4	Physical and Chemical Properties of 2-Butoxyethanol Acetate	284
5-1	Occupational Exposures to 2-Butoxyethanol by Work Site or Process	307
5-2	Estimated Occupational and General Exposure to 2-Butoxyethanol	311
6-1	Analytical Methods for Determining 2-Butoxyethanol, 2-Butoxyethanol Acetate, and Metabolites in Biological Samples	320
6-2	Analytical Methods for Determining 2-Butoxyethanol, 2-Butoxyethanol Acetate, and Metabolites in Environmental Samples	324
7-1	Regulations and Guidelines Applicable to 2-Butoxyethanol and 2-Butoxyethanol Acetate	328

1. PUBLIC HEALTH STATEMENT

This public health statement tells you about 2-butoxyethanol and 2-butoxyethanol acetate and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. 2-Butoxyethanol has been found in at least 20 of the 1,430 current or former NPL sites. 2-Butoxyethanol acetate has not been found at any of the 1,430 current or former NPL sites. However, the total number of NPL sites evaluated is not known. As more sites are evaluated, the sites at which 2-butoxyethanol or 2-butoxyethanol acetate are found may increase. This is important because exposure to these substances may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact.

If you are exposed to 2-butoxyethanol or 2-butoxyethanol acetate, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT ARE 2-BUTOXYETHANOL AND 2-BUTOXYETHANOL ACETATE?

2-Butoxyethanol (bu-tox-zi-eth-an-ol) has many names, including ethylene glycol monobutyl ether, ethylene glycol butyl ether, ethylene glycol *n*-butyl ether, Butyl Cellosolve, butyl glycol, butyl Oxitol, glycol butyl ether, Dowanol EB, Gafcol EB, Poly-solv EB, and Ektasolve EB. Common abbreviations for 2-butoxyethanol include BE and EGBE. It is a clear, colorless liquid

1. PUBLIC HEALTH STATEMENT

that smells somewhat like ether. Most people can begin to smell 2-butoxyethanol in air at 0.10-0.40 parts of 2-butoxyethanol per million parts of air (ppm). These levels are about 500 times lower than the present standard for worker exposure. 2-Butoxyethanol has been found in air, water, and soil as a contaminant. It is completely soluble in water and in most organic solvents. This means that when 2-butoxyethanol and water or 2-butoxyethanol and organic solvents are mixed, the mixtures form one layer, unlike mixing oil and water which separate into two layers. 2-Butoxyethanol is a fire hazard when exposed to heat, sparks, or open flames.

2-Butoxyethanol in the environment comes from some industrial activities. It is usually produced by a reaction of ethylene oxide with butyl alcohol, but it may also be made by the reaction of ethylene glycol with dibutyl sulfate. 2-Butoxyethanol is widely used as a solvent in protective surface coatings such as spray lacquers, quick-dry lacquers, enamels, varnishes, and latex paints. It is also used as an ingredient in paint thinners and strippers, varnish removers, agricultural chemicals, herbicides, silicon caulks, cutting oils, and hydraulic fluids. It has other uses in metal cleaners, fabric dyes and inks, industrial and household cleaners (as a degreaser), and dry-cleaning compounds. It is also used in liquid soaps and in cosmetics.

The acetate (ass-e-tate) form of this chemical is 2-butoxyethanol acetate. It is also known as ethylene glycol monobutyl ether acetate, butoxyethyl acetate, butyl glycol acetate, ethylene glycol butyl ether acetate, acetic acid 2-butoxyethyl ester, glycol monobutyl ether acetate, Butyl Cellosolve acetate, or Ektasolve EB acetate. Common abbreviations for 2-butoxyethanol acetate include BEA and EGBEA. 2-Butoxyethanol acetate has been found in air, water, and soil as a contaminant. It is a colorless liquid with a fruity odor. Most people can begin to smell 2-butoxyethanol acetate in air at 0.10-0.48 ppm. It is only moderately soluble in water but is soluble in most organic solvents. This means that when 2-butoxyethanol acetate and water or 2-butoxyethanol and organic solvents are mixed, the mixtures form one layer, unlike mixing oil and water which separate into two layers. 2-Butoxyethanol acetate is a fire hazard when exposed to heat, sparks, flames, or oxidizers.

1. PUBLIC HEALTH STATEMENT

2-Butoxyethanol acetate in the environment also comes from some industrial activities. It is prepared by reacting 2-butoxyethanol with acetic acid, acetic acid anhydride, or acetic acid chloride. 2-Butoxyethanol acetate is widely used as a slow-evaporating solvent for lacquers, varnishes, epoxy resins, and enamels. It is also used in polyvinyl acetate latex, and it may be used in some ink and spot remover formulations.

For more information on the nature and uses of 2-butoxyethanol and 2-butoxyethanol acetate, see Chapters 3 and 4.

1.2 WHAT HAPPENS TO 2-BUTOXYETHANOL OR 2-BUTOXYETHANOL ACETATE WHEN THEY ENTER THE ENVIRONMENT?

2-Butoxyethanol may be released into the environment at places where it is produced or used as a solvent. Solvent-based household cleaners or building materials such as varnishes, lacquers, latex paints, and enamels may release 2-butoxyethanol into the air as they dry. Municipal landfills and hazardous waste sites can also release 2-butoxyethanol to water that is under the ground.

2-Butoxyethanol can pass into air from water and soil. In the atmosphere, 2-butoxyethanol probably exists almost entirely as a vapor. Once in the air, 2-butoxyethanol may be removed by precipitation (rain, snow, ice) or may break down to other compounds within a few days.

2-Butoxyethanol breaks down more slowly in water and soil than it does in air. It can move out of contaminated soil and move into groundwater. 2-Butoxyethanol does not build up in plants and animals. For more information on what happens to 2-butoxyethanol after it gets into the environment, see Chapter 5.

2-Butoxyethanol acetate can pass into air from water and soil. It is directly released to the atmosphere by evaporation while it is being used as a solvent in paints, lacquers, thinners, inks, ink and spot removers, and resins. 2-Butoxyethanol acetate probably exists almost entirely as a vapor in outdoor air. It can be removed from the air by precipitation because it is moderately soluble in water. In air, 2-butoxyethanol acetate may also break down to other compounds within a few days. 2-Butoxyethanol acetate breaks down more slowly in water and soil than it does in

1. PUBLIC HEALTH STATEMENT

air. It can move out of contaminated soil and move into groundwater. 2-Butoxyethanol acetate does not build up in plants and animals. For more information on what happens to 2-butoxyethanol acetate after it gets into the environment, see Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO 2-BUTOXYETHANOL OR 2-BUTOXYETHANOL ACETATE?

Many people are exposed to small amounts of 2-butoxyethanol and 2-butoxyethanol acetate every day. You can be exposed to these chemicals in the environment, in the workplace, and at home. Higher exposures usually occur in the workplace rather than in the environment or at home. The general population is exposed to 2-butoxyethanol and 2-butoxyethanol acetate mainly by breathing air or having skin contact with liquids, particularly household cleaners, that contain these compounds.

You are less likely to be exposed by eating or drinking something that contains 2-butoxyethanol. The Food and Drug Administration has regulations to control its presence as a food contaminant. However, some drinking water supplies have been shown to contain 2-butoxyethanol.

Some people have been poisoned by accidentally or intentionally drinking consumer products such as all-purpose liquid cleaners containing 2-butoxyethanol. Some people who work in silkscreening, printing, furniture production and finishing, asbestos-mastic removal, and housekeeping occupations that use materials containing 2-butoxyethanol have been exposed to this chemical. People who work in spray-painting operations, chemical production facilities, automobile repair shops, automobile manufacturing facilities, construction sites, and areas that have recently been remodeled using products that contain 2-butoxyethanol may also be exposed to this compound.

You are most likely to be exposed to 2-butoxyethanol acetate by inhaling the vapors and by skin contact with liquid and vapors. Industrial exposures are most likely through inhalation of vapors, although excessive contact with eyes and skin may also occur. 2-Butoxyethanol acetate is used as a solvent in latex paints, lacquers, epoxy resins, thinners, inks, stains, and varnishes, and in ink and spot removers. People who use these products at work or at home can be exposed by inhaling the

1. PUBLIC HEALTH STATEMENT

vapors or by skin or eye contact. Exposure only occurs while these products are being used or while they are drying.

1.4 HOW CAN 2-BUTOXYETHANOL AND 2-BUTOXYETHANOL ACETATE ENTER AND LEAVE MY BODY?

2-Butoxyethanol and 2-butoxyethanol acetate can enter your body through your lungs when you breathe them. They can also enter your body through your stomach and intestines when you eat food or drink water that contains either one. They can enter your body through skin contact with liquid products such as paints, varnishes, ink and spot removers, and household cleaners. If your skin comes in contact with vapors of these compounds in the air, some can also enter your body through your skin. The amount of vapor that enters through your skin is much less than the amount that enters through your lungs, especially if most of your skin is covered by clothing.

When you are exposed to high levels of 2-butoxyethanol or 2-butoxyethanol acetate in air, some of the compound you breathe in leaves your body when you breathe out. The remainder passes through the lining of your lungs and enters your bloodstream. Both can also enter your bloodstream from your intestines if you swallow them. They can enter your bloodstream through your skin if your skin comes into contact with cleaning products containing them or with the vapors in the air. The amount of vapor that enters through your skin is much less than the amount that enters through your lungs, especially if most of your skin is covered by clothing. Once in your bloodstream, 2-butoxyethanol and 2-butoxyethanol acetate travel through your body to many organs and tissues, but they don't stay there very long. 2-Butoxyethanol and 2-butoxyethanol acetate are converted to products, called metabolites, in the liver. Scientists think that some of the effects of exposure to these chemicals are caused by metabolites. Most of the metabolites of 2-butoxyethanol and 2-butoxyethanol acetate leave the body in the urine within 24-48 hours after exposure. Smaller amounts of metabolites leave the body in exhaled air and in the feces. For more information on how 2-butoxyethanol and 2-butoxyethanol acetate can enter and leave your body, see Chapter 2.

1. PUBLIC HEALTH STATEMENT

1.5 HOW CAN 2-BUTOXYETHANOL OR 2-BUTOXYETHANOL ACETATE AFFECT MY HEALTH?

After exposure to 2-butoxyethanol or 2-butoxyethanol acetate, several factors determine whether harmful health effects will occur and, if they do, what the type and severity of these health effects might be. These factors include the amount of 2-butoxyethanol or 2-butoxyethanol acetate to which you are exposed and the length of time of the exposure. Other factors that must be considered include the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

Some information about potential effects on people comes from an experiment in which men and women were exposed continuously to about 100 ppm or more of 2-butoxyethanol vapors in air for 4 or 8 hours. This level is twice as high as the occupational standard for 2-butoxyethanol. Some of these people reported irritation of the nose and eyes, headache, a metallic taste, or vomiting. None of these people had effects on blood pressure or pulse. In another experiment, people were exposed to 20 ppm of 2-butoxyethanol vapors in air for 2 hours. Lung tests (pulmonary function) and heart tests (heart rate and electrocardiogram) showed no harmful effects for any of these people. Exposure to these solvents in the workplace involves both breathing in of vapors and skin contact with the liquids and vapors. Workers are usually exposed to much higher levels than the levels normally encountered by the general population.

Some information on harmful effects also comes from case reports of people who swallowed large amounts of cleaning agents containing 2-butoxyethanol. These harmful effects included breathing problems, low blood pressure, lowered levels of hemoglobin (the substance in the blood that carries oxygen to organs of the body), blood in the urine, and metabolic acidosis (high levels of acid in the body). The lowered levels of hemoglobin and blood in the urine indicate effects related to hemolysis, which involves destruction of red blood cells that results in the release of hemoglobin. Some of these people fell into a coma but recovered after successful treatment in hospitals. People should keep household products containing 2-butoxyethanol out of the reach of children.

1. PUBLIC HEALTH STATEMENT

There are no data on whether 2-butoxyethanol or 2-butoxyethanol acetate cause reproductive effects, birth defects, or cancer in people.

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Other information on the harmful effects of 2-butoxyethanol and 2-butoxyethanol acetate comes from animal testing. The harmful effect most often reported in animals exposed to 2-butoxyethanol is destruction of red blood cells that results in the release of hemoglobin, which is known as hemolysis. Effects related to hemolysis include increased hemoglobin levels in the urine, blood in the urine, and the build-up of hemoglobin and destroyed red blood cells in organs such as the kidney, spleen, and liver. These effects have been found in monkeys, rats, mice, rabbits, and dogs after exposure to high levels of 2-butoxyethanol in air for short and intermediate periods. These effects have also been found in rats and mice that swallowed high doses of 2-butoxyethanol for short and intermediate periods, and in rats and rabbits with skin contact for short periods. 2-Butoxyethanol acetate also caused these effects in rats or rabbits that breathed, swallowed, or had skin contact with 2-butoxyethanol acetate. Some studies showed that the red blood cells of animals (rats, rabbits, and baboons) are much more likely to be destroyed than the red blood cells of people after exposure to 2-butoxyethanol.

Other harmful effects of 2-butoxyethanol have been seen in animals. Breathing problems occurred in rats and mice that breathed or swallowed large amounts of 2-butoxyethanol for short periods.

1. PUBLIC HEALTH STATEMENT

Bloody or reddened stomach or intestines, probably related to hemolysis, were seen in rats that swallowed very high doses of 2-butoxyethanol and in rabbits that had skin contact with very large amounts. Harmful effects on the liver and kidney were seen in some animals and may be related to hemolysis. 2-Butoxyethanol is also irritating to the skin and eyes of animals, as it is in people.

2-Butoxyethanol and 2-butoxyethanol acetate do not seem to have effects on the immune system of animals. Like many solvents, 2-butoxyethanol causes nervous system effects in animals. Some rats, dogs, and rabbits developed physical weakness and unsteadiness after exposure to very high levels of 2-butoxyethanol in air for short periods. Some rats and mice also became sluggish, drowsy, or prostrate after swallowing very large doses of 2-butoxyethanol for short periods. Some rabbits also became inactive or prostrate, had abnormal eye movement, or had convulsions after skin contact with very large amounts of 2-butoxyethanol.

2-Butoxyethanol can cause reproductive effects and birth defects in animals. Some female rats and rabbits that breathed in large amounts of 2-butoxyethanol while they were pregnant delivered fewer offspring than pregnant rats or rabbits that were not exposed. Some of the offspring had underdeveloped bones. Other reproductive effects and birth defects in animals have only been observed at doses that were toxic to the adult animals. Some female rats had changes in their estrous cycles after drinking water containing 2-butoxyethanol for moderate periods of time. Some female rats and mice had vaginal bleeding and fewer offspring after swallowing large doses of 2-butoxyethanol while they were pregnant. Some of the offspring of pregnant mice that swallowed very large doses had cleft palates. Some offspring of pregnant mice that swallowed large doses of 2-butoxyethanol also weighed less.

2-Butoxyethanol does not seem to cause mutations. No studies were found that tested either 2-butoxyethanol or 2-butoxyethanol acetate for causing cancer in animals.

1. PUBLIC HEALTH STATEMENT

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 2-BUTOXYETHANOL OR 2-BUTOXYETHANOL ACETATE?

Some tests can show whether you have been exposed to 2-butoxyethanol or 2-butoxyethanol acetate. 2-Butoxyethanol (from 2-butoxyethanol or 2-butoxyethanol acetate exposure) can be measured in blood and urine. In the body, both are converted to products called metabolites, such as 2-butoxyacetic acid. Certain metabolites of 2-butoxyethanol (2-butoxyacetic acid and others) can be measured in the urine. These tests will not necessarily be able to tell how much you have been exposed to. These tests need to be done within a day after exposure because 2-butoxyethanol and its metabolites leave your body within 24-48 hours. Certain blood tests can determine if your red blood cells are damaged, but this effect is not specific for 2-butoxyethanol. Some of these tests may be available at your doctor's office, or your doctor can send blood or urine samples to laboratories that specialize in performing these tests. If workers are exposed to concentrations of 5 ppm or above, the National Institute for Occupational Safety and Health recommends that the level of 2-butoxyacetic acid in the urine be measured. For more information on tests for 2-butoxyethanol exposure, see Chapters 2 and 6.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect

1. PUBLIC HEALTH STATEMENT

people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for 2-butoxyethanol include the following:

OSHA requires employers of workers who are occupationally exposed to 2-butoxyethanol to institute engineering controls and work practices to reduce and maintain employee exposure at or below the permissible exposure limit (PEL). The PEL for 2-butoxyethanol is 50 ppm. This regulation means that the workroom air should not contain no more than an average of 50 ppm of 2-butoxyethanol over an 8-hour working shift of a 40-hour work week. The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended an average concentration limit value of 25 ppm for occupational exposure (8-hour workday and a 40-hour workweek) to 2-butoxyethanol. The recommended exposure limit (REL) for occupational exposure by NIOSH is 5 ppm for both 2-butoxyethanol and 2-butoxyethanol acetate. This recommendation means that the workroom air should contain no more than an average of 5 ppm of 2-butoxyethanol or 2-butoxyethanol acetate for up to a 10-hour working shift of a 40-hour workweek. OSHA recommends that workers who may be exposed to 2-butoxyethanol should wear personal protective equipment such as gloves, coveralls, and goggles to protect against exposure to the skin and eyes.

Both 2-butoxyethanol and 2-butoxyethanol acetate are regulated under the Clean Air Act, including the National Emission Standards for Hazardous Air Pollutants.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

1. PUBLIC HEALTH STATEMENT

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: 1-800-447- 1544
Fax: (404) 639-6315

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact:

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 487-4650

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 2-butoxyethanol and 2-butoxyethanol acetate. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure—inhalation, oral, and dermal; and then by health effect—death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods—acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in Figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of

2. HEALTH EFFECTS

the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for 2-butoxyethanol. Insufficient data were available to estimate MRLs for 2-butoxyethanol acetate. Since 2-butoxyethanol acetate is metabolized to the same toxic metabolite as is 2-butoxyethanol, it seems likely that the MRLs for 2-butoxyethanol acetate would be similar to those of 2-butoxyethanol. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2. HEALTH EFFECTS

2.2.1 inhalation Exposure

Occupational or environmental exposure to 2-butoxyethanol or 2-butoxyethanol acetate usually occurs through inhalation or dermal contact. Both routes of exposure are important in the industrial setting. Occupational exposure to 2-butoxyethanol usually involves co-exposure to other solvents and chemicals. In several NIOSH Health Hazard Evaluations, effects reported by workers included eye, nose, and throat irritation; coughing; runny nose; headache; dizziness; lightheadedness; and nausea (Apol 1981,1986; Lee 1988). Since personal breathing zone and workplace air samples analyzed for solvents and other chemicals, such as toluene, xylene, methyl ethyl ketone, methyl isobutyl ketone, styrene, along with 2-butoxyethanol, indicated that exposure levels for each chemical were below the NIOSH, ACGIH, and OSHA criteria, NIOSH concluded that the effects were probably due to the additive combination of the solvents. Experimental studies in which humans were exposed to 2-butoxyethanol by the inhalation route, in addition to experimental animal studies, are discussed in this section (Section 2.2.1) and have been summarized in several publications (Browning and Curry 1994; EPA 1984; NIOSH 1990; Tyler 1984). Although one study was located regarding oral exposure of animals to the major metabolite of 2-butoxyethanol, 2-butoxyacetic acid (discussed in Section 2.2.2), no studies were located describing the effects of 2-butoxyacetic acid after inhalation exposure.

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to 2-butoxyethanol or 2-butoxyethanol acetate.

The amount of 2-butoxyethanol in air required to produce death in animals has been measured under a variety of conditions. Acute 4-hour LC₅₀ (lethal concentration, 50% kill) values for Fischer 344 rats after wholebody exposure were determined to be 486 ppm for males and 450 ppm for females (Dodd et al. 1983). In another study, a 4-hour LC₅₀ for rats was reported to be 500 ppm (Nelson et al. 1984). In addition, in a preliminary concentration-finding study, in which non-pregnant female Sprague-Dawley rats were exposed to 2-butoxyethanol for 6.5 or 7 hours, death occurred in three of four rats at 450-500 ppm, in two of three rats at 350 ppm, and in two of three rats at 250 ppm for 7 hours (Nelson et al. 1984). Male Fischer 344 rats exposed to 2-butoxyethanol by nose-only inhalation at 438 ppm 2-butoxyethanol for 6 hours exhibited 50% (two of four) mortality (Sabourin et al. 1992a). Carpenter et al. (1956) observed death in rats at ≥ 375 ppm for 1-3 days (7 hours per day) and at 314 ppm for up to 30 days (7 hours per day, and 5 days per week). No

2. HEALTH EFFECTS

deaths occurred in rats similarly exposed to ≤ 203 ppm for 30 days. Similarly, when Fischer 344 rats were exposed to concentrations of 0, 20, 86, or 245 ppm of 2-butoxyethanol for 9 days, 6 hours per day, 4-5 days per week, no rats died during the exposure period or the 14-day observation period (Dodd et al. 1983). Sprague-Dawley rats exposed to 682 ppm 2-butoxyethanol for 3 hours showed no mortality during the exposure or the 14-day postexposure observation period (Khmisch et al. 1988). Similarly, no Fischer 344 rats died after 13 weeks of exposure to 77 ppm 2-butoxyethanol for 5 days per week, 6 hours per day (Dodd et al. 1983). An inhalation LC_{50} of 700 ppm was reported for mice exposed to 2-butoxyethanol for 7 hours (Werner et al. 1943a). C3H mice exhibited 20% (2 of 10) mortality after continuous exposure to 376 ppm 2-butoxyethanol and 70% (7 of 10) mortality after continuous exposure to 494 ppm for 30 days (no controls were used), although the same strain of mice exposed to ≤ 400 ppm for 90 days exhibited no mortality (Carpenter et al. 1956). Guinea pigs seem to be less sensitive to the lethal effects of 2-butoxyethanol and exhibited no mortality after exposure to 691 ppm for 1 hour followed by a 14-day observation period (Nachreiner 1994) or to 411 ppm for up to 5 days (Dow 1986). However, Carpenter et al. (1956) reported death in 1 of 10 guinea pigs exposed to 376 ppm and in 2 of 10 guinea pigs exposed to 494 ppm for 7 hours per day, 5 days per week, for a total of 30 days. No deaths occurred at ≤ 203 ppm. Some studies in dogs have reported mortality at concentrations of 385-617 ppm, with exposures of 2-8 days or 28 days (Carpenter et al. 1956), whereas other reports indicate no mortality in dogs at concentrations that are similar or lower (Dow 1972, 1986). The studies in dogs used only one or two dogs per exposure level and sometimes did not include a control dog. Rabbits exhibited mortality at concentrations ≥ 200 ppm after exposure for 6 or 7 hours per day for 1-13 days (Dow 1986; Tyl et al. 1984).

No deaths were noted in Wistar rats exposed to a saturated vapor-air mixture of approximately 400 ppm 2-butoxyethanol acetate for 4 hours; 400 ppm for 1 month, 5 days per week, 4 hours per day; or 100 ppm for 10 months using the same intermittent exposure regimen (Truhaut et al. 1979). No deaths were observed in New Zealand white rabbits exposed to 400 ppm 2-butoxyethanol acetate for 4 hours or to 100 ppm 2-butoxyethanol acetate for 10 months under the same regimen as the rats. However, two of four rabbits died after exposure to 400 ppm 2-butoxyethanol acetate for 1 month, 5 days per week, 4 hours per day (Truhaut et al. 1979).

The LC_{50} values for rats and all LOAEL values from each reliable study for death for each species and duration category for 2-butoxyethanol and 2-butoxyethanol acetate are recorded in Tables 2-1 and 2-2 and plotted in Figures 2-1 and 2-2, respectively.

Table 2-1. Levels of Significant Exposure to 2-Butoxyethanol - Inhalation

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
ACUTE EXPOSURE							
Death							
1	Rat (NS)	1-6 d 2-9 hr/d				375 (death of 11/13 males and 23/23 females after 7 hrs)	Carpenter et al. 1956
2	Rat (Sherman)	3 d 7 hr/d				432 F (15/15 died)	Carpenter et al. 1956
3	Rat (Fischer- 344)	4 hr				486 M (LC ₅₀) 450 F (LC ₅₀)	Dodd et al. 1983
4	Rat (Sprague- Dawley)	1 d 6.5 -7hr				250 F (2/3 died)	Nelson et al. 1984
5	Rat (Fischer- 344)	6 hr				438 M (2/4 died)	Sabourin et al. 1992a
6	Mouse (Swiss)	7 hr				700 (LC ₅₀)	Werner et al. 1943a
7	Rabbit (albino)	1-2d 7 hr/d				400-411 M (25-100% death)	Dow 1986
8	Rabbit (New Zealand)	Gd 6-18 6 hr/d				200 F (4/24 died)	Tyl et al. 1984
Systemic							
9	Human	4-8 hr	Resp	98	113 (nasal irritation, slight increase in nasal mucus discharge)		Carpenter et al. 1956
			Cardio	195 M			
			Gastro		98 F (emesis)		
			Hemato	195			
			Ocular	98	113 (ocular irritation)		
10	Human	2 hr	Resp	20 M			Johanson et al. 1986a
			Cardio	20 M			

Table 2-1. Levels of Significant Exposure to 2-Butoxyethanol - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
11	Rat (NS)	2-8 hr	Hemato			432 F (hemolysis in 2 hrs; hemoglobinuria in 3 hrs; hemin crystals in urine in 4 hrs)	Carpenter et al. 1956
			Renal		432 F (slight cloudy swelling of convoluted tubules in 2 hrs)		
12	Rat (NS)	9 d 7 hr/d	Hemato			200 F (50% decrease in erythrocyte count and 25% decrease in HGB level)	Carpenter et al. 1956
13	Rat (NS)	4 hr	Hemato	32 F	62 F (significant osmotic fragility of RBCs)		Carpenter et al. 1956
14	Rat (Fischer- 344)	4 hr	Resp	523	867 (rapid and shallow breathing)		Dodd et al. 1983
			Renal	202		523 (red discharge around urogenital area and bladder [hematuria]; enlarged kidneys)	

Table 2-1. Levels of Significant Exposure to 2-Butoxyethanol - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference	
					Less serious (ppm)	Serious (ppm)		
15	Rat (Fischer- 344)	9 d 5 d/wk 6 hr/d	Resp	86 M	245 M (audible respiration and nasal discharge)		Dodd et al. 1983	
			Hemato	245 F				
				20	86 M (HGB decreased 5%, significant increases in MCV of 11%) 86 F (HGB decreased 8%, MCHC decreased 18%, significant increases in MCV of 17%)			
			Hepatic	86 M	245 M (increased liver weights of about 5.4%)			
				20 F	86 F (increased liver weights of about 4.5%)			
			Renal	86	245 (transient red-stained urine [hematuria])			
			Ocular Bd Wt	245				
86 M	245 M (13% decrease in body weight gain)							
	20 F	86 F (10% decrease in body weight gain)						
16	Rat (Alpk/Ap)	3 hr	Renal			800 M (hematuria)	Doe 1984	
17	Rat (Sprague-Dawley)	4 d 7 hr/d	Bd Wt	57-58 M			Dow 1972	
18	Rat (Sprague-Dawley)	Gd 7-15 7 hr/d	Renal			150 F (slight hematuria)	Nelson et al. 1984	
19	Rat (Sprague-Dawley)	1 d 6.5 -7 hr	Renal				250 F (hematuria)	Nelson et al. 1984
			Dermal				250 F (necrotic tail tip)	

Table 2-1. Levels of Significant Exposure to 2-Butoxyethanol - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
20	Rat (Fischer- 344)	6 hr	Hemato			438 M (hemoglobinuria)	Sabourin et al. 1992a
21	Rat (Fischer- 344)	Gd 6-15 6 hr/d	Resp	50 F	100 F (perinasal encrustation)		Tyl et al. 1984
			Hemato	50 ^b F		100 F (reduced RBC and MCHC; increased MCH and MCV)	
			Hepatic	200 F			
			Renal	50 F		100 F (hematuria)	
			Dermal	100 F	200 F (necrosis of the tail tip, stained fur)		
			Ocular		25 F (periocular wetness)		
			Bd Wt	50 F		100 F (29% decrease in body weight gain)	
			Other	50 F	100 F (13% reduction in food consumption)		
				100 F	200 F (14% reduction in water consumption)		
22	Mouse (NS)	7 hr	Hemato		100 (increased osmotic fragility)		Carpenter et al. 1956
23	Mouse (Swiss- Webster)	10 min	Resp		153M (20% decrease in respiratory rate)		Kane et al. 1980
24	Gn Pig (NS)	8 hr	Hemato	665 M			Carpenter et al. 1956
25	Rabbit (NS)	7 hr	Hemato		125 (increased osmotic fragility of RBCs)		Carpenter et al. 1956

Table 2-1. Levels of Significant Exposure to 2-Butoxyethanol - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
26	Rabbit (albino)	1-2d 7 hr/d	Resp			400-411 M (congestion of lungs and turbinates, nasal discharge)	Dow 1986
			Gastro Hepatic		400- M (mottled livers in 411 surviving animals)	400-411 M (hemorrhagic gastric ulcers)	
			Renal			400-411 M (darkened kidneys in surviving animals, hematuria)	
			Ocular		400- M (ocular discharge, 411 yellowing of sclerae)		
27	Rabbit (New Zealand)	Gd 6-18 6 hr/d	Resp	100 F	200 F (perinasal wetness and discharge)		Tyl et al. 1984
			Hemato	50 F	100 F (increased hemoglobin and hematocrit)		
			Hepatic	200 F			
			Renal	50 F		100 F (hematuria)	
			Dermal	100 F	200 F (stained fur)		
			Ocular	50 F	100 F (periocular wetness)		
			Bd Wt	100 F	200 F (9.7% reduction in maternal body weight)		
			Immunological/Lymphoreticular				
28	Rat (Fischer- 344)	Gd 6-15 6 hr/d		100 F	200 F (20-24% increase in absolute and relative maternal spleen weights)		Tyl et al. 1984
Neurological							
29	Human	4-8 hr			98 (headache)		Carpenter et al. 1956
				98	113 M (disagreeable metallic taste)		
30	Rat (Fischer- 344)	4 hr		202		523 (loss of coordination)	Dodd et al. 1983

Table 2-1. Levels of Significant Exposure to 2-Butoxyethanol - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
31	Dog (Beagle)	1-5 d 7 hr/d			400-411 M (salivation)		Dow 1986
32	Rabbit (albino)	1-2 d 7 hr/d				400- M (poor coordination of 411 extremities and loss of equilibrium)	Dow 1986
Reproductive							
33	Rat (Fischer- 344)	Gd 6-15 6 hr/d		100 F		200 F (50% decrease in viable implants & in live fetuses per litter; 8-fold increase in nonviable implants; reduced maternal gravid uterine weight)	Tyl et al. 1984
34	Rabbit (New Zealand)	Gd 6-18 6 hr/d		100		200 F (14% decrease in total implants; 20% decrease in viable implants)	Tyl et al. 1984
Developmental							
35	Rat (Sprague- Dawley)	Gd 7-15 7 hr/d		200			Nelson et al. 1984
36	Rat (Fischer- 344)	Gd 6-15 6 hr/d		50	100	(retarded skeletal ossification)	Tyl et al. 1984
37	Rabbit (New Zealand)	Gd 6-18 6 hr/d		100	200	(22% reduction in gravid uterine weight, reduced ossification in fetuses)	Tyl et al. 1984
INTERMEDIATE EXPOSURE							
Death							
38	Rat (Sherman)	30 d 5 d/wk 7 hr/d				432 M (12/15 died) 314 F (15/15 died)	Carpenter et al. 1956
39	Mouse (C3H)	30 d				376 M (2/10 died)	Carpenter et al. 1956

Table 2-1. Levels of Significant Exposure to 2-Butoxyethanol - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
40	Gn Pig (NS)	30 d 5 d/wk 7 hr/d				376 M (1/10 died)	Carpenter et al. 1956
Systemic							
41	Rat (Sherman)	30 d 5 d/wk 7 hr/d	Resp	203		432 M (congestion & hemorrhage 314 F of the lungs)	Carpenter et al. 1956
			Gastro	203		432 M (congestion of the 314 F abdominal viscera)	
			Hemato		54 (erythrocyte fragility)	203 (hemoglobinuria)	
			Hepatic	54	107 (unspecified increase in liver weight)		
			Renal	54	107 (unspecified increase in kidney weight)		
			Bd Wt	203			
42	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Resp	77			Dodd et al. 1983.
			Cardio	77			
			Hemato	25 ^c		77 (5%-13% decrease in RBC, in both sexes; 4% decrease in HGB; 11% increase in MCH, females)	
			Musc/skel	77			
			Hepatic	77			
			Renal	77			
			Endocr	77			
			Bd Wt	77			
43	Mouse (C3H)	30-90 d 7 hr/d	Hemato		100 M (increased erythrocyte osmotic fragility)		Carpenter et al. 1956
			Hepatic	100 M	200 M (unspecified increase (p<0.05) in liver weights)		
			Renal	400 M			
			Bd Wt	200 M	400 M (unspecified decrease (p<0.05) in body weights)		

Table 2-1. Levels of Significant Exposure to 2-Butoxyethanol - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
44	Gn Pig (NS)	30 d 5 d/wk 7 hr/d	Resp	203 M	376 M (lung congestion)		Carpenter et al. 1956
			Hemato	494 M			
			Hepatic	494 M			
			Renal	107 M	203 M (unspecified increase (p<0.05) in kidney weight)		
			Bd Wt	495 M			
45	Dog (Hybrid)	31 d	Resp		200	(slight capillary engorgement or breakdown in the lungs)	Carpenter et al. 1956
			Hemato			200 M (increased osmotic fragility of RBCs and 100% increased leukocyte counts)	
					200 F (RBC osmotic fragility increased slightly; slight decrease in RBC count and hemoglobin level)		
			Ocular	200			
46	Dog (Terrier)	90 d	Hemato		100	(decreased hematocrit in male, transitory doubling of the leukocyte count midway into the 90-day exposure in both sexes)	Carpenter et al. 1956

Table 2-1. Levels of Significant Exposure to 2-Butoxyethanol - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
47	Dog (NS)	12 wk 5 d/wk 7 hr/d	Resp		415	(slightly increased nasal secretions)	Werner et al. 1943b
			Cardio	415			
			Gastro	415			
			Hemato		415	(decreased Hgb, hematocrit; hypochromia, polychromatophilia, and microcytosis)	
			Hepatic	415			
			Renal	415			
			Ocular		415	(slight increased secretions in the eyes)	
Immunological/Lymphoreticular							
48	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		77			Dodd et al. 1983
Neurological							
49	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		77			Dodd et al. 1983
Reproductive							
50	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		77 M			Dodd et al. 1983
CHRONIC EXPOSURE							
Systemic							
51	Human	1-6 yr	Hemato	0.6 ^d M			Haufroid et al. 1997
			Hepatic	0.75 M			
			Renal	0.75 M			

Table 2-1. Levels of Significant Exposure to 2-Butoxyethanol - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	

^aThe number corresponds to entries in Figure 2-1. Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 2-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

^bUsed to derive an acute inhalation minimal risk level (MRL) of 6.0 ppm. Concentration converted to an equivalent concentration in humans, and divided by an uncertainty factor of 9 (3 for extrapolation from animals to humans and 3 for human variability). For further details, see MRL worksheets in Appendix A.

^cUsed to derive an intermediate inhalation MRL of 3.0 ppm. Concentration converted to an equivalent concentration in humans, and divided by an uncertainty factor of 9 (3 for extrapolation from animals to humans and 3 for human variability). For further details, see MRL worksheets in Appendix A.

^dUsed to derive a chronic inhalation MRL of 0.2 ppm. Concentration divided by an uncertainty factor of 3 for human variability. Hematocrit significantly [p=0.03] decreased to 43.9%, MCHC significantly [p=0.02] increased to 33.6 g/dL. Changes in hematocrit and MCHC were within the range of normal clinical values and therefore were considered NOAELs. These effects were consistent with hemolysis seen in animal studies and may be an early indicator of potential adverse effects in humans. For further details, see MRL worksheets in Appendix A.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestational day; Gn Pig = guinea pig; Hemato = hematological; HGB = hemoglobin; hr = hour(s); LC₅₀ = lethal concentration; 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular concentration; MCV = mean corpuscular volume; min = minute(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; RBC = red blood cell; Resp = respiratory; wk = week(s).

Table 2-2. Levels of Significant Exposure to 2-Butoxyethanol Acetate - Inhalation

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
ACUTE EXPOSURE							
Systemic							
1	Rat (Wistar)	4 hr	Resp	400			Truhaut et al. 1979
			Cardio	400			
			Hemato	400			
			Hepatic	400			
			Renal	400			
			Endocr	400			
2	Rabbit (New Zealand)	4 hr	Resp	400			Truhaut et al. 1979
			Cardio	400			
			Hemato		400	(slight and transient hemoglobinuria)	
			Hepatic	400			
			Renal		400	(slight and transient hematuria)	
			Endocr	400			
INTERMEDIATE EXPOSURE							
Death							
3	Rabbit (New Zealand)	1 mo 5 d/wk 4 hr/d				400 (death in 2/4)	Truhaut et al. 1979

Table 2-2. Levels of Significant Exposure to 2-Butoxyethanol Acetate - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
Systemic							
4	Rat (Wistar)	1 mo 5 d/wk 4 hr/d	Resp	400			Truhaut et al. 1979
			Cardio	400			
			Hemato			400 (hemoglobinuria)	
			Hepatic	400			
			Renal		400 M (slight hematuria)	400 F (slight hematuria; in females tubular nephrosis, cellular cloudy swelling to hemorrhagic necrosis)	
			Endocr	400			
	Bd Wt	400					
5	Rat (Wistar)	10 mo 5 d/wk 4 hr/d	Resp	100			Truhaut et al. 1979
			Cardio	100			
			Hemato	100			
			Hepatic	100			
			Renal			100 M (discrete and inconstant lesions - tubular nephritis; enlargement; atrophy; inflammatory fibrosis; dilatated Henle's loop, distal convoluted tubules; hyaline casts)	
			Endocr	100 F			
	Bd Wt	100					

Table 2-2. Levels of Significant Exposure to 2-Butoxyethanol Acetate - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
6	Rabbit (New Zealand)	1 mo 5 d/wk 4 hr/d	Resp	400			Truhaut et al. 1979
			Cardio Hemato	400		400 (28-59% decrease in RBC, 24-62% decrease in HGB concentration; pronounced hemoglobinuria)	
			Hepatic Renal	400		400 (hypertrophy, necrotizing tubular nephrosis, atrophic tubular dilatation, luminal granular deposits; hematuria)	
			Endocr Bd Wt	400 400			
7	Rabbit (New Zealand)	10 mo 5 d/wk 4 hr/d	Resp	100			Truhaut et al. 1979
			Cardio Hemato Hepatic Renal	100 100 100		100 (tubular nephritis with tubular enlargement, cortical atrophy, inflammatory fibrosis, dilatation of Henle's loop and distal convoluted tubules)	
			Endocr Bd Wt	100 100			
8	Rat (Wistar)	1 mo 5 d/wk 4 hr/d	Immunological/Lymphoreticular				Truhaut et al. 1979
				400			

Table 2-2. Levels of Significant Exposure to 2-Butoxyethanol Acetate - Inhalation (continued)

Key to figure ^a	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
9	Rat (Wistar)	10 mo 5 d/wk 4 hr/d		100			Truhaut et al. 1979
10	Rabbit (New Zealand)	10 mo 5 d/wk 4 hr/d		100			Truhaut et al. 1979
11	Rabbit (New Zealand)	1 mo 5 d/wk 4 hr/d		400			Truhaut et al. 1979
Neurological							
12	Rat (Wistar)	1 mo 5 d/wk 4 hr/d		400			Truhaut et al. 1979
13	Rat (Wistar)	10 mo 5 d/wk 4 hr/d		100			Truhaut et al. 1979
14	Rabbit (New Zealand)	10 mo 5 d/wk 4 hr/d		100			Truhaut et al. 1979
15	Rabbit (New Zealand)	1 mo 5 d/wk 4 hr/d		400			Truhaut et al. 1979
Reproductive							
16	Rat (Wistar)	1 mo 5 d/wk 4 hr/d		400			Truhaut et al. 1979

Table 2-2. Levels of Significant Exposure to 2-Butoxyethanol Acetate - Inhalation (continued)

Key to ^a figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
17	Rat (Wistar)	10 mo 5 d/wk 4 hr/d		100			Truhaut et al. 1979
18	Rabbit (New Zealand)	10 mo 5 d/wk 4 hr/d		100			Truhaut et al. 1979
19	Rabbit (New Zealand)	1 mo 5 d/wk 4 hr/d		400			Truhaut et al. 1979

^aThe number corresponds to entries in Figure 2-2.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; Hemato = hematological; HGB = hemoglobin; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; M = male; mo = month(s); NOAEL = no-observable-adverse-effect level; RBC = red blood cell; Resp = respiratory; wk = week(s).

Figure 2-1. Levels of Significant Exposure to 2-Butoxyethanol - Inhalation
Acute (≤ 14 days)

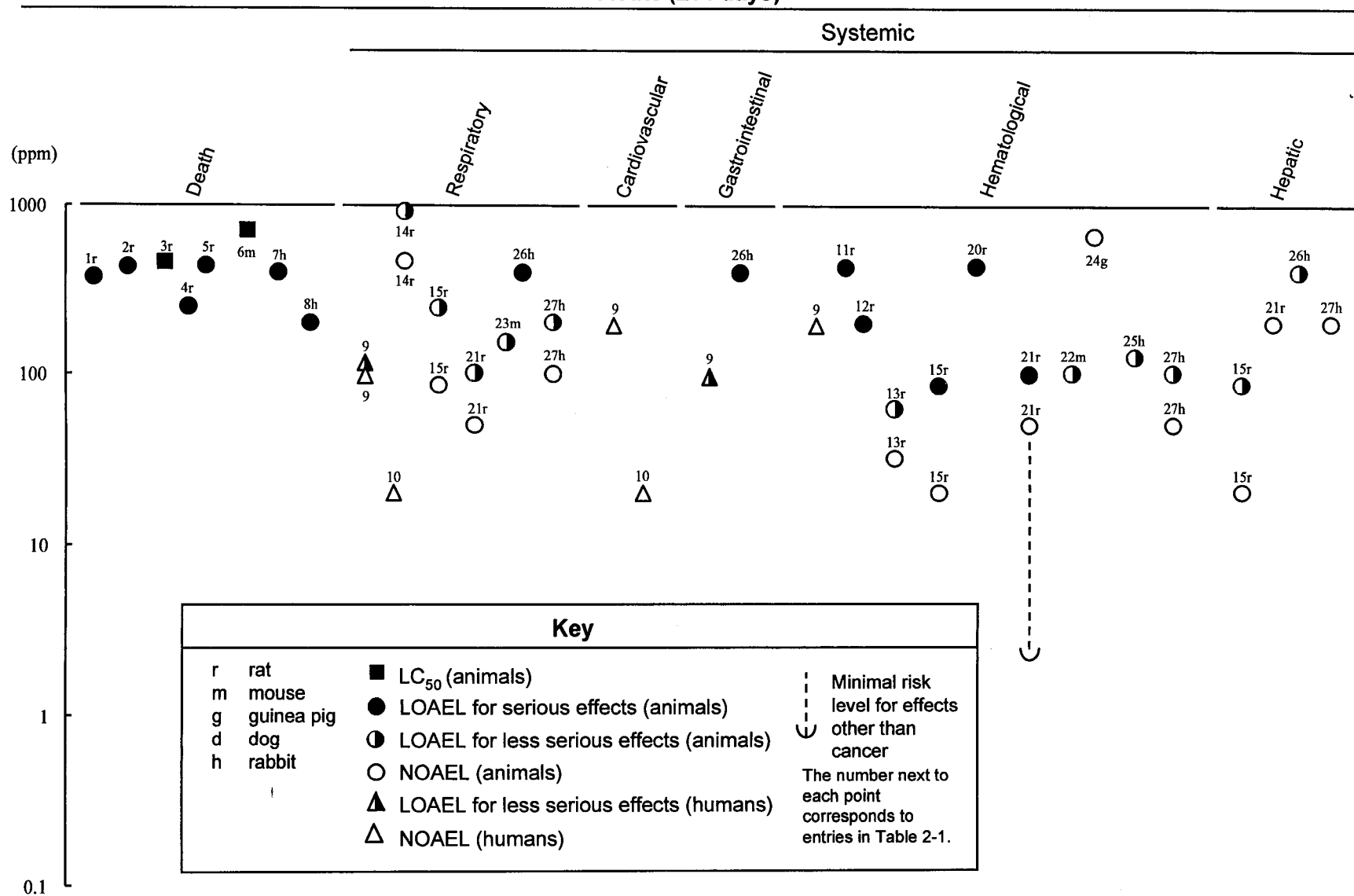


Figure 2-1. Levels of Significant Exposure to 2-Butoxyethanol - Inhalation (cont.)
Acute (≤ 14 days)

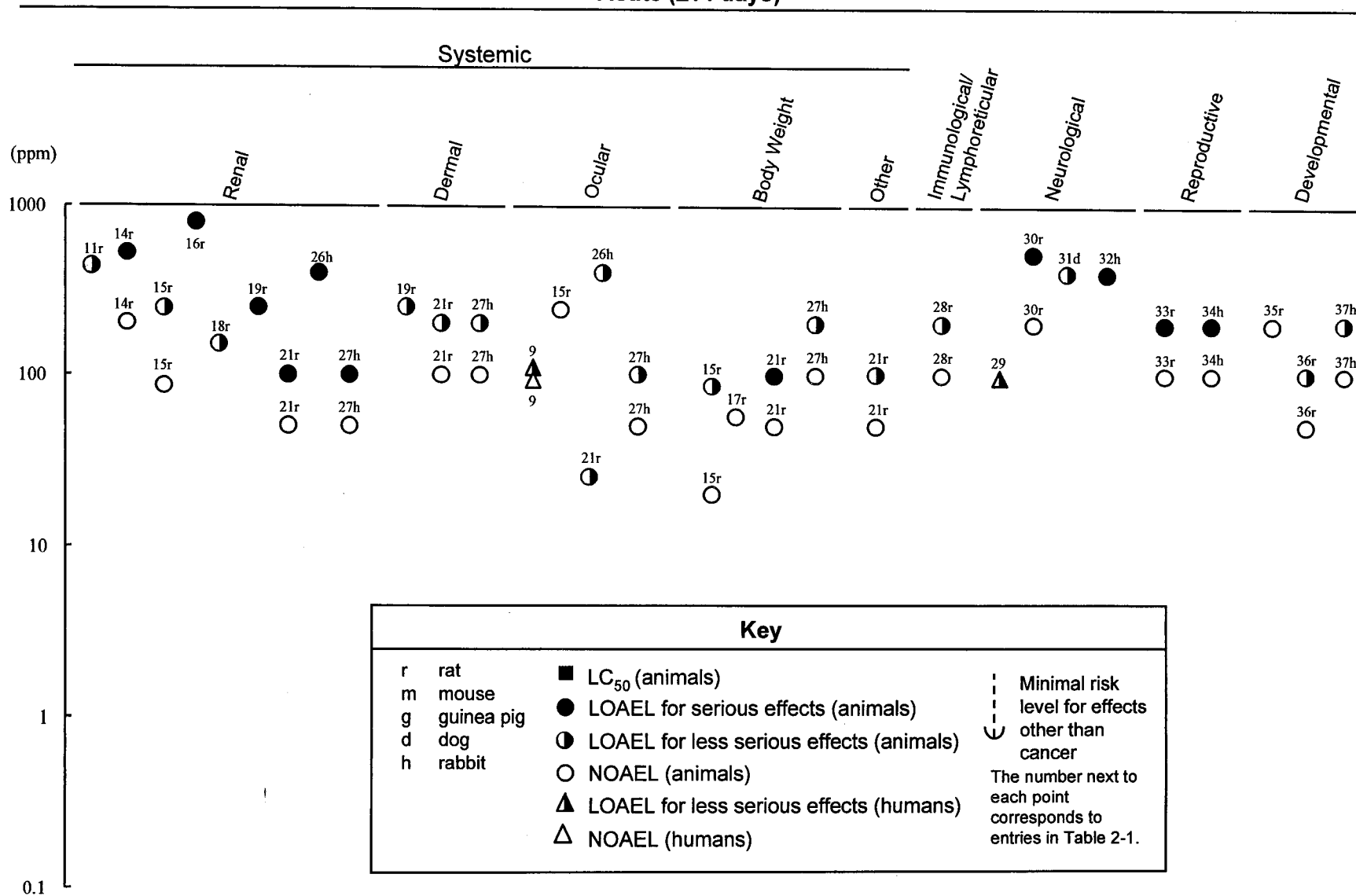


Figure 2-1. Levels of Significant Exposure to 2-Butoxyethanol - Inhalation
Intermediate (15-364 days)

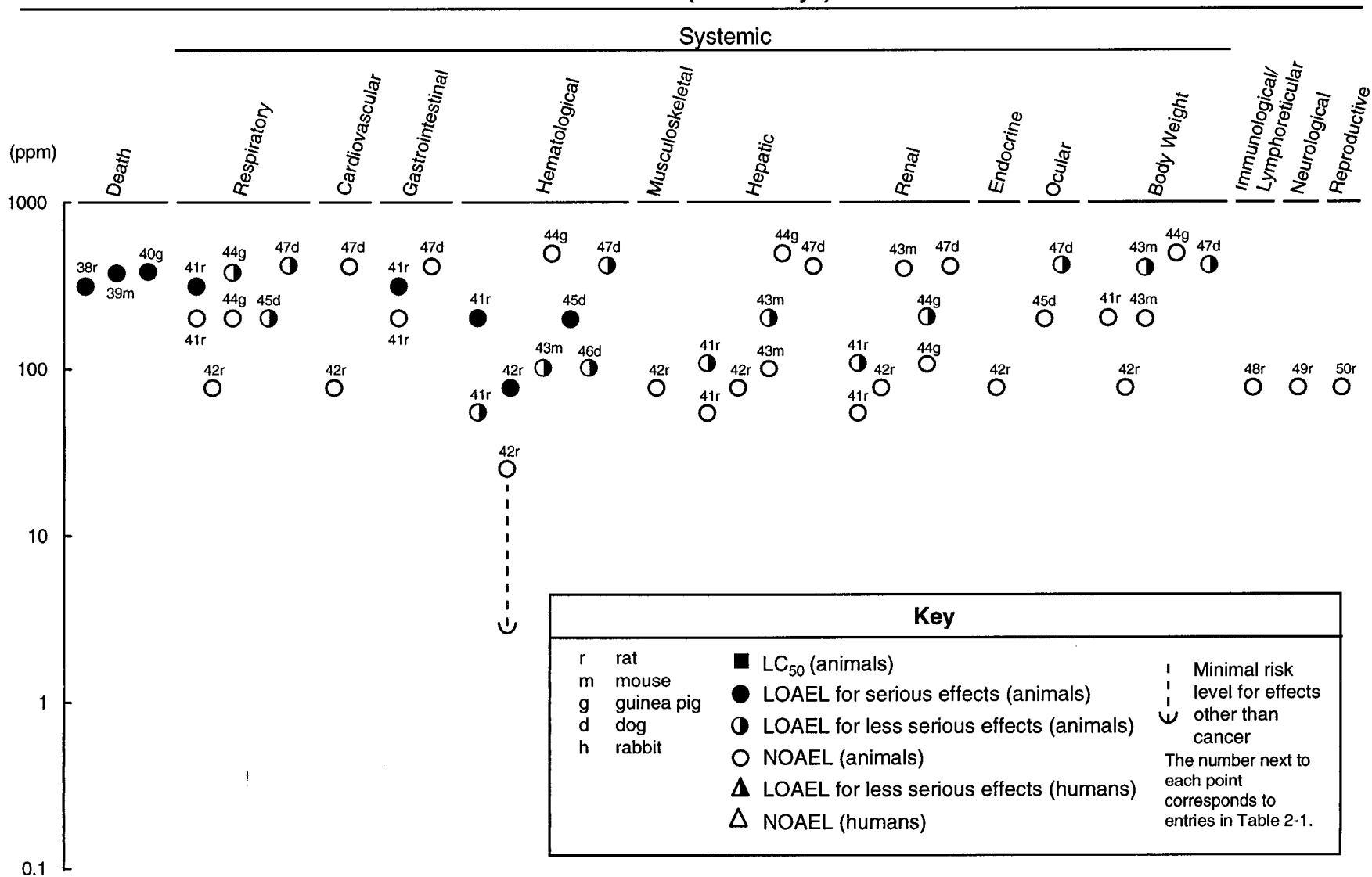


Figure 2-1. Levels of Significant Exposure to 2-Butoxyethanol - Inhalation

Chronic (≤ 365 days)

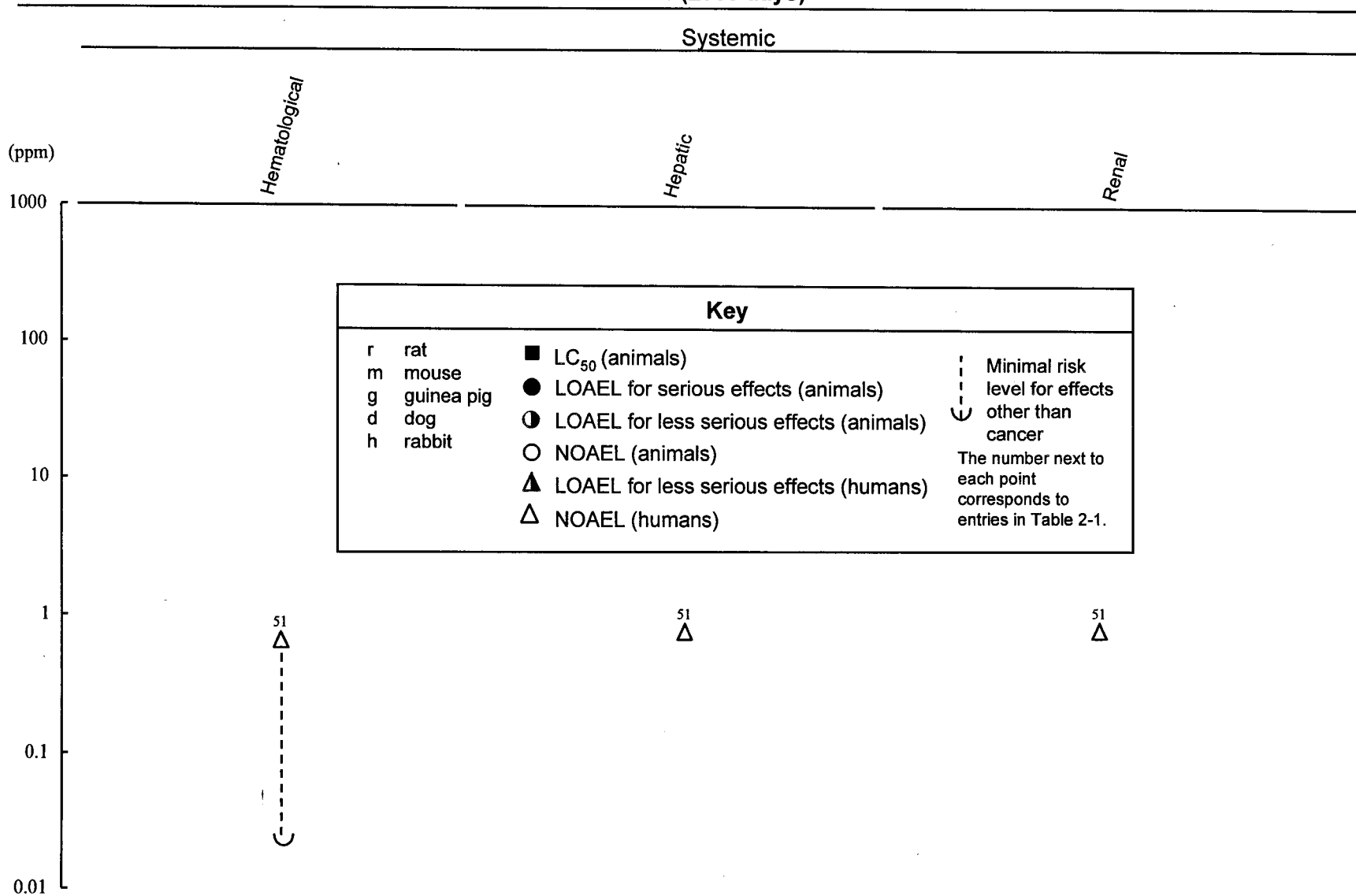


Figure 2-2. Levels of Significant Exposure to 2-Butoxyethanol Acetate - Inhalation

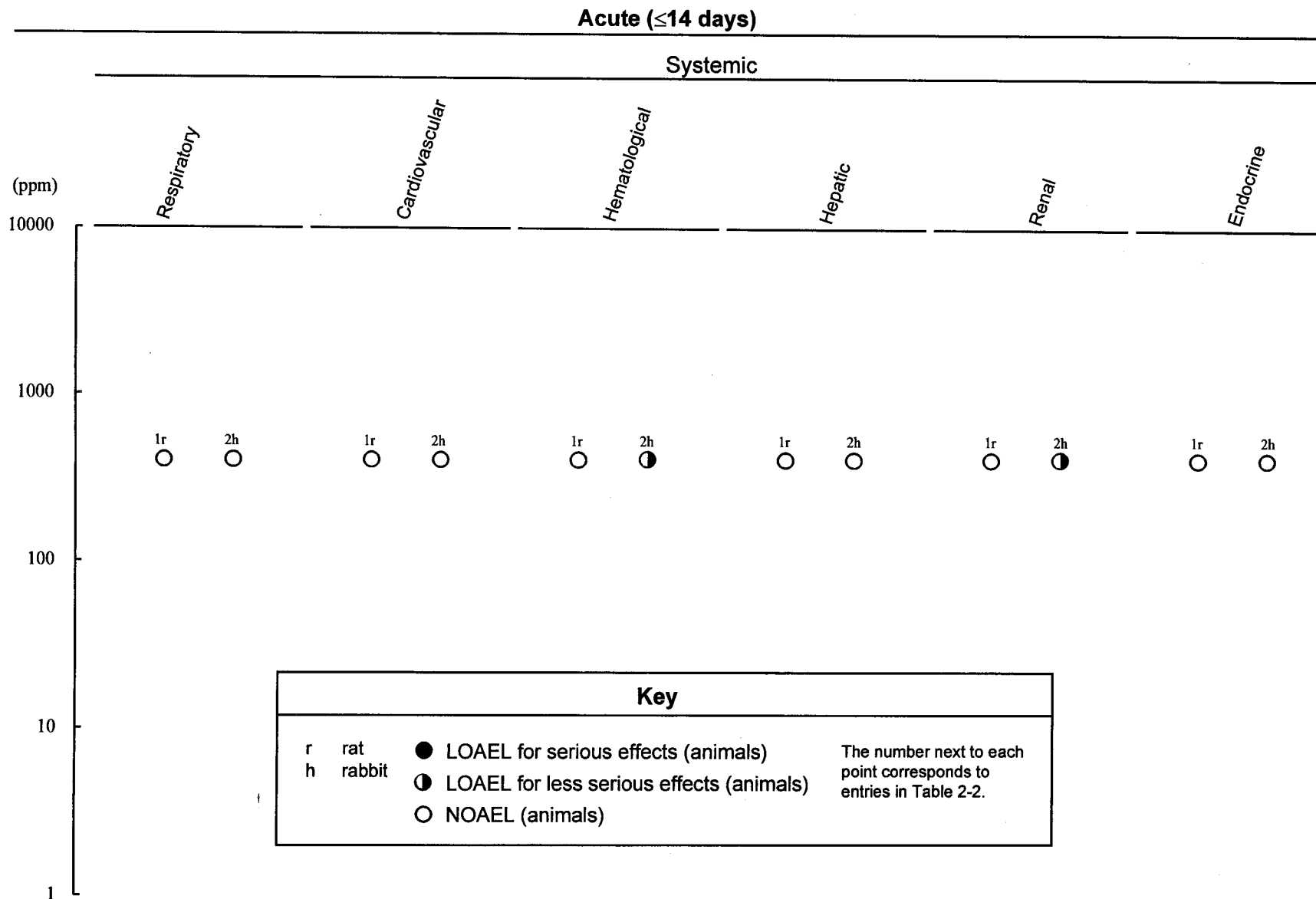


Figure 2-2. Levels of Significant Exposure to 2-Butoxyethanol Acetate - Inhalation (cont.)
Intermediate (15-364 days)

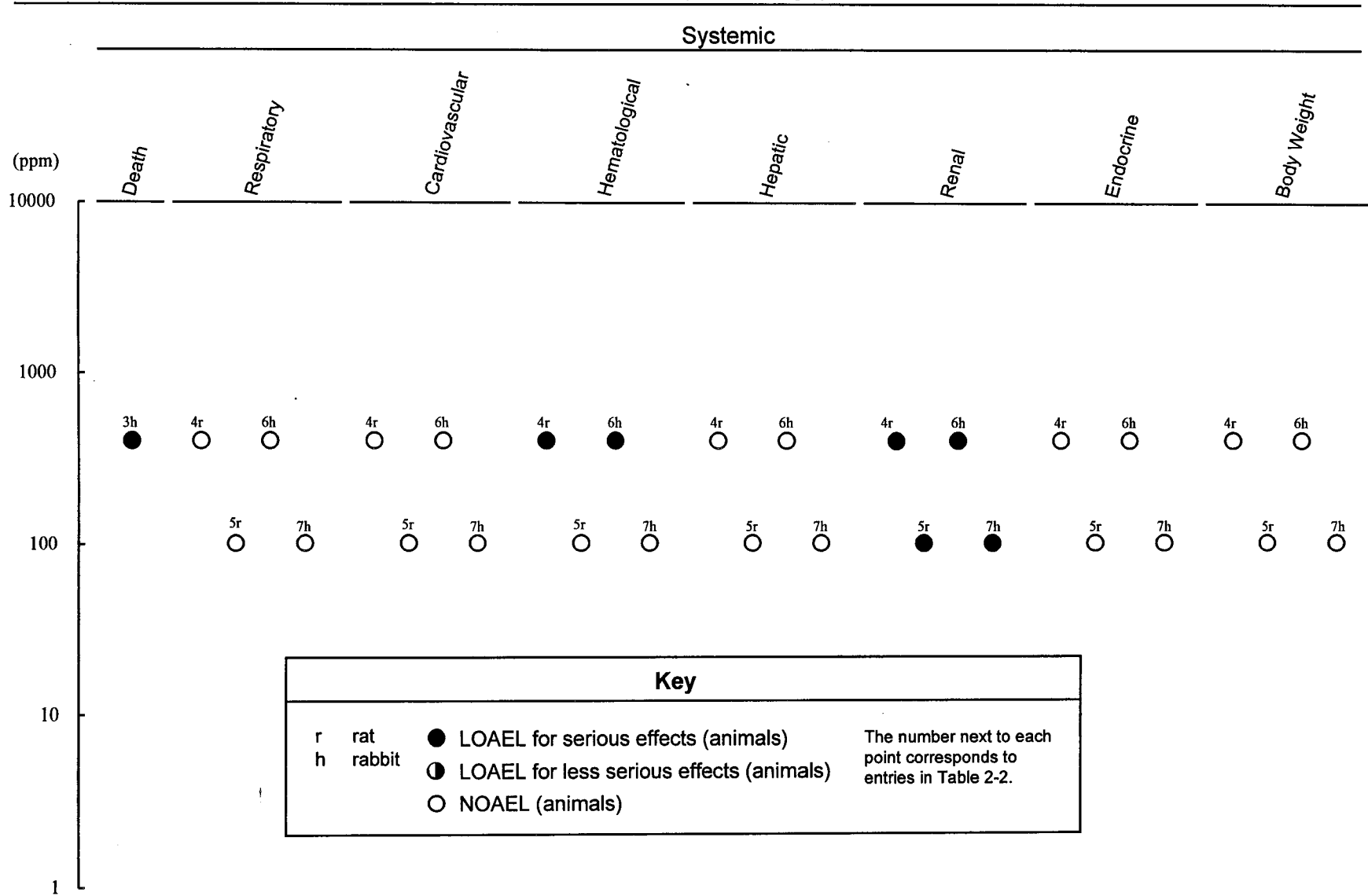
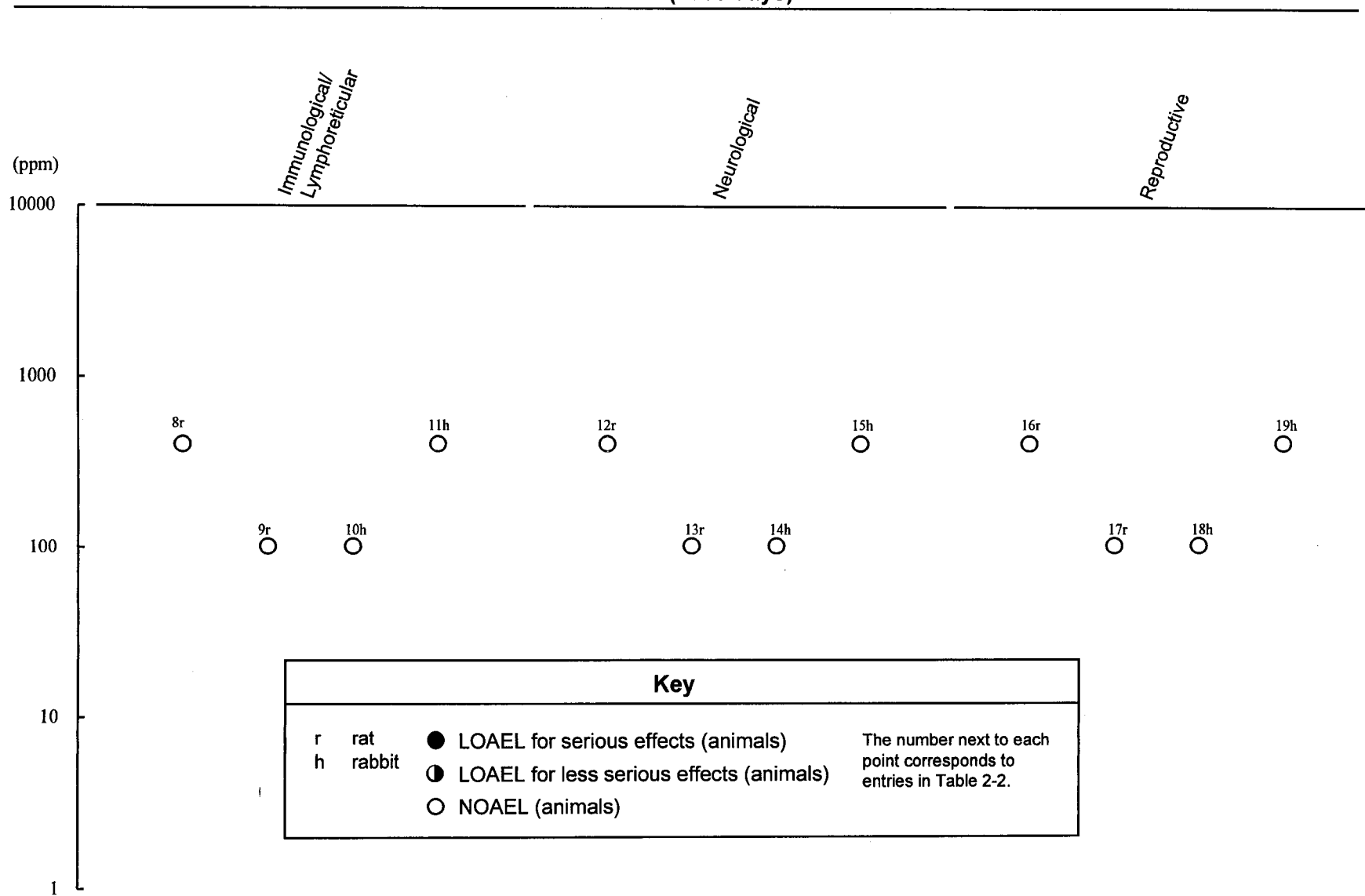


Figure 2-2. Levels of Significant Exposure to 2-Butoxyethanol Acetate - Inhalation (cont.)

Chronic (≥ 365 days)



2. HEALTH EFFECTS

2.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal, endocrine, dermal, or body weight effects in humans after inhalation exposure to 2-butoxyethanol. No studies were located regarding any systemic effects in humans, or regarding gastrointestinal, musculoskeletal, dermal, or ocular effects in animals after inhalation exposure to 2-butoxyethanol acetate. Available data pertaining to systemic effects of each compound are presented below.

The highest NOAEL values and all reliable LOAEL values from each reliable study for systemic effects in each species and duration category for each compound are recorded in Tables 2-1 and 2-2 and plotted in Figures 2-1 and 2-2.

Respiratory Effects. Volunteers were exposed to 98, 113, or 195 ppm 2-butoxyethanol for 4-8 hours (Carpenter et al. 1956). The recorded responses of those exposed to 195 ppm included immediate irritation of the nose and throat. The subjects exposed to 113 ppm also experienced nasal irritation and a slight increase in nasal mucus discharge. In another study, no effects on pulmonary ventilation or respiratory frequency were found in seven male volunteers exposed to 2-butoxyethanol for 2 hours at the Swedish occupational exposure limit (20 ppm) during light physical exercise on a bicycle ergometer (Johanson et al. 1986a).

Respiratory effects have been observed in animals exposed to 2-butoxyethanol by inhalation for acute durations. In Fischer 344 rats exposed for 4 hours to 0, 202, 523, or 867 ppm 2-butoxyethanol, rapid and shallow breathing, followed by death, occurred at 867 ppm (Dodd et al. 1983). No respiratory effects were observed at ≤ 523 ppm. In the same study, Fischer 344 rats exposed for 9 days, 6 hours per day, 5 days per week to 2-butoxyethanol at 0, 20, 86, or 245 ppm exhibited audible respiration and nasal discharge in a few male animals only at 245 ppm (Dodd et al. 1983). Perinatal encrustation was noted in timed-pregnant female Fischer 344 rats exposed to 2-butoxyethanol concentrations of 100 or 200 ppm for 6 hours per day on gestational days 6-15 (Tyl et al. 1984). Male Swiss Webster mice exposed to a range of concentrations of 153-1,666 ppm 2-butoxyethanol for 10-15 minutes exhibited a 20% decrease in respiratory rate at the lowest concentration and a 40% decrease at the highest concentration (Kane et al. 1980). The decrease in respiration rate occurred during the first few seconds of exposure and is an indicator of respiratory irritation. Male albino rabbits exposed to approximately 400 ppm 2-butoxyethanol for 1-2 days at 7 hours per day exhibited nasal discharge and congestion of the lungs and nasal turbinates upon necropsy (Dow 1986).

2. HEALTH EFFECTS

Wetness around the nose was observed in pregnant New Zealand white rabbits exposed to 200 ppm 2-butoxyethanol for 6 hours per day on gestational days 6-18 (Tyl et al. 1984). One female dog exposed repeatedly to 617 ppm 2-butoxyethanol for a total of 13.5 hours over 2 days exhibited moderate congestion of the lungs upon necropsy (Carpenter et al. 1956). Similarly, a female dog exposed to 385 ppm 2-butoxy-ethanol for 8 days died and was found to have severely congested and hemorrhagic lungs at necropsy. Clinical signs and gross necropsy observations did not reveal any adverse respiratory effects in guinea pigs exposed to 691 ppm (females) or 633 ppm (males) 2-butoxyethanol for 1 hour followed by a 14-day observation period (Nachreiner 1994).

In intermediate-duration studies of 2-butoxyethanol, Fischer 344 rats exposed intermittently to 77 ppm for 13 weeks showed no effects on lung weight and no histopathological lesions in the lungs (Dodd et al. 1983), while Sherman rats exposed to 2-butoxyethanol for 7 hours per day, 5 days per week, for a total 30 days exhibited congested and hemorrhagic lungs at necropsy at 432 ppm (males) and 314 ppm (females) (Carpenter et al. 1956). Guinea pigs also exhibited lung congestion at necropsy after intermittent exposure to ≥ 376 ppm 2-butoxyethanol for 30 days (Carpenter et al. 1956). Severely congested and hemorrhagic lungs were found in one dog exposed to 385 ppm for 28 days, and slight capillary engorgement or breakdown in the lungs was observed upon gross necropsy (not confirmed by histological examination) of two dogs exposed to 200 ppm for 31 days (Carpenter et al. 1956). Slightly increased nasal secretions were observed in two dogs exposed to 415 ppm 2-butoxyethanol 17 hours per day, 5 days per week, for 12 weeks (Werner et al. 1943b). One rhesus monkey exposed to 210 ppm 2-butoxyethanol for up to 30 days and two rhesus monkeys exposed to 100 ppm for 90 days exhibited no respiratory effects (Carpenter et al. 1956).

In a study of 2-butoxyethanol acetate, Wistar rats and New Zealand white rabbits were exposed to a saturated vapor-air mixture of approximately 400 ppm for 4 hours, and then observed for 14 days after exposure (Truhaut et al. 1979). No clinical signs of respiratory distress were noted for either species. When the animals were sacrificed at the end of 2 weeks, no gross pathological lesions were observed in respiratory tissues of either rats or rabbits. No histological examinations were performed. In the intermediate-duration experiments in this study, in which both gross and histological examinations were performed, no respiratory effects were noted in either rats or rabbits after intermittent exposure (5 days per week, 4 hours per day) to 400 ppm 2-butoxyethanol acetate for 1 month or to 100 ppm 2-butoxyethanol acetate for 10 months (Truhaut et al. 1979).

2. HEALTH EFFECTS

Cardiovascular Effects. No adverse cardiovascular effects were observed in male volunteers exposed to 20 ppm 2-butoxyethanol for 2 hours during light physical exercise on a bicycle ergometer (Johanson et al. 1986a). Specifically, no effects of exposure were noted for heart rate, and no effects were noted in the electrocardiograms. In an earlier study, male and female volunteers exposed to 98, 113, or 195 ppm 2-butoxyethanol for 4-8 hours showed no adverse effects on blood pressure or pulse rate (Carpenter et al. 1956).

Gross necropsy did not reveal any changes in the hearts of guinea pigs exposed to 2-butoxyethanol for 1 hour followed by a 14-day observation period at 691 ppm for females and 633 ppm for males (Nachreiner 1994). No gross or histological lesions in the heart were observed in male or female Fischer 344 rats exposed to 77 ppm 2-butoxyethanol for 6 hours per day, 7 days per week, for 13 weeks (Dodd et al. 1983) or in two dogs exposed to 415 ppm 7 hours per day, 5 days per week, for 12 weeks (Werner et al. 1943b)

In a study of 2-butoxyethanol acetate, Wistar rats and New Zealand white rabbits were exposed to a saturated vapor-air mixture of approximately 400 ppm 2-butoxyethanol acetate for 4 hours and were then observed for 14 days after exposure (Truhaut et al. 1979). When the animals were sacrificed at the end of 2 weeks, no gross pathological lesions were observed in the hearts of either rats or rabbits. No histological examinations were performed. In the intermediate-duration experiments in this study, in which both gross and histological examinations were performed, no lesions in the heart were noted in either rats or rabbits after intermittent exposure (5 days per week, 4 hours per day) to 400 ppm 2-butoxyethanol acetate for 1 month or to 100 ppm 2-butoxyethanol acetate for 10 months (Truhaut et al. 1979).

Gastrointestinal Effects. Two male volunteers exposed to 113 ppm 2-butoxyethanol for 4 hours experienced occasional belching (eructation), while a female volunteer exposed to 98 ppm for 8 hours experienced emesis after 7 hours of exposure and several times on the following day, although other male and female volunteers exposed to the same or higher concentrations did not react similarly (Carpenter et al. 1956). The subject who experienced emesis, however, believed that the emesis was due to the relatively high chamber temperature based on her personal past experience that high temperature often caused emesis.

One female dog, exposed repeatedly to 617 ppm 2-butoxyethanol for a total of 13.5 hours during 2 days, experienced emesis on both days of exposure (Carpenter et al. 1956). Similarly, a female dog exposed to 385 ppm 2-butoxyethanol for 8 days experienced emesis several times during the first 4 days of exposure and died on the 8th day (Carpenter et al. 1956). Gross examination of the gastrointestinal tract did not reveal

2. HEALTH EFFECTS

adverse effects in guinea pigs exposed to 2-butoxyethanol at 691 ppm (females) or 633 ppm (males) for 1 hour followed by a 14-day observation period (Nachreiner 1994). Male albino rabbits exposed to approximately 400 ppm 2-butoxyethanol for 1-2 days at 7 hours per day exhibited hemorrhagic gastric ulcers upon necropsy (Dow 1986). One rhesus monkey exposed to 210 ppm 2-butoxyethanol for up to 30 days exhibited emesis four times during the latter part of the exposure period (Carpenter et al. 1956). Sherman rats exposed to 2-butoxyethanol for 7 hours per day, 5 days per week, for a total 30 days exhibited congestion of the abdominal viscera at necropsy at 432 ppm for males and 314 ppm for females (Carpenter et al. 1956). Emesis and histopathological changes in the small and large intestines were not observed in two dogs exposed to 2-butoxyethanol at 415 ppm for 7 hours per day, 5 days per week, for 12 weeks (Werner et al. 1943b).

Hematological Effects. Although hematological effects of 2-butoxyethanol exposure in animals include hemolysis, hemoglobinuria, and hemoglobin in the urine resulting from lysed red blood cells (Jones and Hunt 1983), the only information regarding hematological effects in humans after inhalation exposure to 2-butoxyethanol is negative. Male and female volunteers exposed to 98, 113, or 195 ppm 2-butoxyethanol for 4-8 hours showed no adverse effect on erythrocyte osmotic fragility (Carpenter et al. 1956).

Red blood cell counts, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, heptoglobin, reticulocytes, and osmotic resistance were measured in 31 male workers exposed to 2-butoxyethanol for 1-6 years (Haufroid et al. 1997). Twenty of the workers were exposed to an average concentration of 0.75 ppm, and 11 workers were exposed to an average concentration of 0.46 ppm. The geometric mean exposure concentration for the 31 workers was 0.6 ppm. The workers were also exposed to unspecified concentrations of methyl ethyl ketone. Studies in animals indicate that methyl ethyl ketone does not produce hematologic effects (ATSDR 1992). Twenty-one unexposed workers from the same plant matched for sex, age and smoking habits served as controls; however, 2-butoxyethanol concentrations in the air the controls breathed was not assayed. Urine was collected before the shift and at the end of the shift and assayed for free 2-butoxyacetic acid (thought to be the toxic metabolite), retinol binding protein, and creatinine. Rettenmeier et al. (1993) and Sakai et al. (1994) found that some of the 2-butoxyacetic acid (BAA) in the urine of humans is excreted as amino acid conjugates. Thus, free BAA in urine does not represent all internal dosing. Blood was collected and assayed for red blood cell counts, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, haptoglobin, reticulocytes, and osmotic resistance. Serum alanine aminotransferase and aspartate aminotransferase were also measured. The exposed workers wore

2. HEALTH EFFECTS

gloves, thus minimizing dermal exposure. In addition, two exposure groups were combined together for the analysis of measured parameters. A significant correlation ($r = 0.55$, $p = 0.0012$) was observed between end shift free urinary 2-butoxyacetic acid concentrations and 2-butoxyethanol in air. There was no effect on red blood cell numeration, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, heptoglobin, reticulocyte (aspartate aminotransferase, alanine aminotransferase) and renal (plasma creatinine, urinary retinol binding protein) parameters. Two small but statistically significant differences in hematology values were observed: a significant decrease ($p=0.03$) in hematocrit values (exposed $43.9\% \pm 2.1$, range: 39.9-50.7; controls: $45.5\% \pm 2.7$, range: 40.6-50.4) and a significant ($p=0.02$) increase in mean corpuscular hemoglobin concentration ($33.6 \text{ g/dL} \pm 0.9$, range: 31.8-35.6; $32.9 \text{ g/dL} \pm 1.1$, range: 31.1-35.6). The differences may be consistent with hemolysis observed in animal studies, and may be early indicators of potential adverse effects in humans; however, because the changes in both hematocrit and mean corpuscular hemoglobin concentration were in the range of normal clinical values, the effect was considered a NOAEL. Normal clinical values of hematocrit are reported for males as 40-54%, with a level of 30% or less considered to indicate moderate to severe anemia (Fischbach 1992). Normal clinical values of mean corpuscular hemoglobin concentration are reported as 31-37 g hemoglobin/dL (Fischbach 1992). Increased mean corpuscular hemoglobin concentrations often indicate spherocytosis, while decreased mean corpuscular hemoglobin concentrations may indicate macrocytic anemia, chronic blood loss anemia, or pyridoxine-responsive anemia (Fischbach 1992). The study author stated that the usefulness of hematocrit and mean corpuscular hemoglobin concentration as early markers of red blood cell toxicity in workers exposed to low concentrations of 2-butoxyethanol requires further study. Based on the NOAEL of 0.6 ppm for decreased hematocrit and increased mean corpuscular hemoglobin concentration, a chronic-duration inhalation MRL of 0.2 ppm was calculated as described in the footnote to Table 2-1 and in Appendix A.

Hematological effects of 2-butoxyethanol have been observed in animals after acute and intermediate inhalation exposure. One male monkey and one female monkey exposed to 200 ppm 2-butoxyethanol for 7 hours did not show any alteration of erythrocyte fragility or evidence of hemoglobinuria (Carpenter et al. 1956). However, one rhesus monkey exposed to 210 ppm 2-butoxyethanol for up to 30 days exhibited elevated osmotic fragility after the fourth exposure, increased fibrinogen after the 14th day, and reduced erythrocyte count and hemoglobin values after 30 exposures (Carpenter et al. 1956). One male monkey and one female monkey exposed to 100 ppm for 90 days had transiently increased erythrocyte osmotic fragility and decreased numbers of erythrocytes .

2. HEALTH EFFECTS

Female rats exposed to 432 ppm 2-butoxyethanol for 2-8 hours exhibited hemolysis at 2 hours, hemoglobinuria at 3 hours, and hemin crystalluria at 4 hours during exposure, whereas rats exposed to 200 ppm for 7 hours per day for 9 days exhibited a decrease in red blood cell count and hemoglobin level (Carpenter et al. 1956). Elevation of erythrocyte fragility was seen at doses as low as 62 ppm administered to rats for 4 hours, or 54 ppm administered for up to 30 days (Carpenter et al. 1956). In addition, Carpenter et al. (1956) reported hemoglobinuria in rats after inhalation exposure to 203 ppm 2-butoxyethanol for 7 hours; in rats exposed to 250-800 ppm for 2-9 hours per day over 1-6 days; in rats exposed to 203 ppm for 7 hours, 5 days per week for 30 days; and in mice after inhalation exposure to 200 ppm 2-butoxyethanol for 7 hours. Hemoglobinuria was noted in male Fischer 344 rats after 6 hours of exposure to 438 ppm (Sabourin et al. 1992a).

In a study in which mice were exposed to 390-1210 ppm 2-butoxyethanol for 7 hours hemoglobinuria was reported (Werner et al. 1943a). The concentrations at which hemoglobinuria was observed were not stated. Mice exhibited increased osmotic fragility of the red blood cells after 7 hours of exposure to 100 ppm 2-butoxyethanol, as did rabbits after exposure to 125 ppm. However, guinea pigs showed no effect of treatment on erythrocyte fragility after exposure to 665 ppm for 8 hours or to \leq 494 ppm for 7 hours per day 5 days per week for 30 days, and dogs showed no effect after exposure to 665 ppm for 7 hours per day for 2 days (Carpenter et al. 1956). C3H mice exhibited increased erythrocyte fragility after exposure to \geq 100 ppm for 30-90 days, as did one female dog exposed to 385 ppm for 8 days and one male dog exposed to 385 ppm for 28 days (Carpenter et al. 1956). Although the increase in erythrocyte fragility in the dogs was transient, increases in leucocyte count in the male and female dogs and fibrinogen levels in the male dog were also seen (Carpenter et al. 1956). In other experiments, increased osmotic fragility and leucocyte count were seen in one male dog and one female dog after exposure to 200 ppm for 31 days, and increased leucocyte counts were seen after 45 days of exposure to 100 ppm; decreased hematocrit was noted in the male dog throughout the exposure period of 90 days (Carpenter et al. 1956). Decreased hemoglobin and hematocrit, hypochromia, polychromatophilia, and microcytosis were observed in two dogs exposed to 415 ppm 2-butoxyethanol 7 hours per day, 5 days per week, for 12 weeks (Werner et al. 1943b).

Fischer 344 rats were exposed for 9 days, 6 hours per day, 5 days per week to 2-butoxyethanol at 0, 20, 86, or 245 ppm (Dodd et al. 1983). The rats were observed for signs of toxicity during exposure and for 14 days postexposure. There was no effect on the hematologic parameters in rats exposed to 20 ppm 2-butoxyethanol. At the 86-ppm exposure, both sexes exhibited a significant effect on erythroid parameters, including decreased hemoglobin and increased mean corpuscular volume. In addition, mean corpuscular hemoglobin

2. HEALTH EFFECTS

concentration was decreased in females at 86 ppm. At the 245-ppm exposure, both male and female rats showed significantly depressed red blood cell count, hemoglobin, and mean corpuscular hemoglobin concentration and significant increases in mean corpuscular volume, nucleated red blood cell count, and reticulocytes. A 14-day postexposure recovery period showed substantial recovery (Dodd et al. 1983). Timed-pregnant Fischer 344 rats exposed to 2-butoxyethanol vapors by inhalation on gestational days 6-15 at concentrations of 0, 25, 50, 100, or 200 ppm for 6 hours per day exhibited hemoglobinuria, reduced red blood cell count, reduced mean corpuscular hemoglobin concentration, increased mean corpuscular hemoglobin, and increased mean corpuscular volume at 100 ppm, but not at ≤ 50 ppm (Tyl et al. 1984). Hemoglobin concentration and hematocrit were increased at 200 ppm. In the same study, pregnant New Zealand white rabbits exposed on gestational days 6-18 to the same concentrations exhibited increased hemoglobin and hematocrit at 100 ppm but not at 200 ppm, suggesting to the authors a biphasic response of the hematological system in rabbits (Tyl et al. 1984). Based on the NOAEL of 50 ppm for hematological effects in rats in the study by Tyl et al. (1984), an acute inhalation MRL of 6 ppm for 2-butoxyethanol was calculated as described in the footnote to Table 2-1 and in Appendix A.

When rats were exposed to 5, 25, or 77 ppm 2-butoxyethanol 5 days per week, 6 hours per day, for 13 weeks, decreased red blood cell count was observed at 77 ppm in males and females; females also exhibited decreased hemoglobin and mean corpuscular hemoglobin concentration at 77 ppm (Dodd et al. 1983). Thus, 25 ppm is the NOAEL for hematological effects in rats after intermediate-duration inhalation exposure to 2-butoxyethanol. Based on this value, an intermediate inhalation MRL of 3.0 ppm for 2-butoxyethanol was calculated as described in the footnote to Table 2-1 and in Appendix A.

In a study of 2-butoxyethanol acetate, Wistar rats and New Zealand white rabbits were exposed to a saturated vapor-air mixture of approximately 400 ppm 2-butoxyethanol acetate for 4 hours and then observed for 14 days after exposure (Truhaut et al. 1979). No persistent hematological effects were noted for either species, although rabbits exhibited slight, transient hemoglobinuria. When the animals were sacrificed at the end of 2 weeks, no adverse changes in hematology were observed in either rats or rabbits. In the same study, hemoglobinuria was noted in rats beginning 2 weeks after initiation of intermittent exposure (5 days per week, 4 hours per day) to 400 ppm 2-butoxyethanol acetate for 1 month, but no effect was noted in rats or rabbits similarly exposed to 100 ppm for 10 months (Truhaut et al. 1979). Rabbits exposed to 400 ppm 2-butoxyethanol acetate for 1 month exhibited decreased red blood cell counts, decreased hemoglobin concentration, and pronounced hemoglobinuria (Truhaut et al. 1979).

2. HEALTH EFFECTS

The hemolytic effects of 2-butoxyethanol and 2-butoxyethanol acetate are reflected in changes in the spleen. These effects are discussed further in Section 2.2.1.3, Immunological and Lymphoreticular Effects.

Musculoskeletal Effects. Gross lesions in bone (femur, vertebrae, joint, sternum) or skeletal muscle were not observed in guinea pigs exposed to 2-butoxyethanol for 1 hour followed by a 14-day observation period at 661 ppm for females and 633 ppm for males (Nachreiner 1994). In Fischer 344 rats exposed to 0, 5, 25, or 77 ppm 2-butoxyethanol for 6 hours per day, 5 days per week for 13 weeks, no gross or histopathological lesions were found in the gastrocnemius muscle or in the sternum (Dodd et al. 1983).

Hepatic Effects. No effects on serum alanine aminotransferase or aspartate aminotransferase were observed when compared to controls in 31 male workers exposed to 2-butoxyethanol for 1-6 years (Haufrond et al. 1997). Twenty of the workers were exposed to an average concentration of 0.75 ppm, and 11 workers were exposed to an average concentration of 0.46 ppm. The workers were also exposed to unspecified concentrations of methyl ethyl ketone. Twenty-one unexposed workers from the same plant matched for sex, age and smoking habits served as controls.

Fischer 344 rats exposed for 9 days, 6 hours per day, 5 days per week to 2-butoxyethanol at 0, 20, 86, or 245 ppm showed increased liver weight at ≥ 86 ppm in females and at 245 ppm in males (Dodd et al. 1983). Timed-pregnant Fischer 344 rats exposed to 2-butoxyethanol vapors by inhalation on gestational days 6-15 and New Zealand white rabbits exposed on gestational days 6-18 to concentrations of 0, 25, 50, 100, or 200 ppm for 6 hours per day exhibited no effect on liver weight (Tyl et al. 1984). Gross lesions in the liver were not observed in guinea pigs exposed to 2-butoxyethanol (at 661 ppm for females and 633 ppm for males) for 1 hour followed by a 14-day observation period (Nachreiner 1994). In male albino rabbits exposed to 400-411 ppm 7 hours per day for 1 or 2 days, mottled livers were observed upon necropsy (Dow 1986). Congestion of the liver was observed at necropsy in a female dog that died following exposure to 385 ppm 2-butoxyethanol for 8 days and in a male dog exposed to the same concentration for 28 days (Carpenter et al. 1956). Only one female and one male dog (both exposed to 385 ppm) were used in this study.

In intermediate-duration studies, a statistically significant increase in liver weight was observed in Sherman rats exposed to ≥ 107 ppm, 7 hours per day, 5 days per week for 30 days (Carpenter et al. 1956). Cloudy swelling of the liver was observed in the rats exposed to 314 ppm (female) and 432 ppm (male and female). In C3H mice exposed for 7 hours per day, a statistically significant increase in liver weight was observed at

2. HEALTH EFFECTS

200 ppm after 60 exposure days (but not after 30 or 90 days) and at 400 ppm after 30, 60, and 90 days (Carpenter et al. 1956). However, no effects on liver weight and no gross or histologically observed liver lesions were found in guinea pigs exposed to <495 ppm for 7 hours per day, 5 days per week for 30 days. Gross or histopathological changes in the liver were not observed in two dogs exposed to 415 ppm 2-butoxyethanol 7 hours per day, 5 days per week for 12 weeks (Werner et al. 1943b). No effects on clinical blood parameters and no gross or histopathological lesions were found in the livers of Fischer 344 rats exposed to ≤77 ppm 2-butoxyethanol for 6 hours per day, 5 days per week, for 13 weeks (Dodd et al. 1983).

In a study of 2-butoxyethanol acetate, Wistar rats and New Zealand white rabbits exposed to a saturated vapor-air mixture of approximately 400 ppm 2-butoxyethanol acetate for 4 hours, and then observed for 14 days after exposure, had no gross hepatic pathological lesions when the animals were sacrificed at the end of 2 weeks (Truhaut et al. 1979). In the same study, no gross or histologically observed hepatic lesions were noted in either rats or rabbits after intermittent exposure (5 days per week, 4 hours per day) to 400 ppm for 1 month or 100 ppm for 10 months.

Renal Effects. No effects on serum creatinine or urinary retinol binding protein were observed in 31 male workers exposed to 2-butoxyethanol for 1-6 years (Haufrond et al. 1997). Twenty of the workers were exposed to an average concentration of 0.75 ppm, and 11 workers were exposed to an average concentration of 0.46 ppm. The workers were also exposed to unspecified concentrations of methyl ethyl ketone. Twentyone unexposed workers from the same plant matched for sex, age and smoking habits served as controls.

A common renal effect of 2-butoxyethanol exposure is hematuria, the detection of red blood cells in the urine (Jones and Hunt 1983). Section 2.4.2 Mechanisms of Toxicity discusses the mechanism by which this effect may occur. When Fischer 344 rats were exposed for 4 hours to 0, 202, 523, or 867 ppm 2-butoxyethanol, red discharge around the urogenital area was detected at concentrations of 523 and 857 ppm (Dodd et al. 1983). Additionally, rats in the high- and mid-dose groups that died and were necropsied after death had red-stained urine in their bladders (presumably hematuria) and enlarged kidneys. This effect was not observed in the surviving rats in the 523-ppm group necropsied 14 days after exposure ceased. It is likely that the red staining observed in the urogenital area occurred because of hematuria. In the same study, Fischer 344 rats were exposed for 9 days, 6 hours per day, 5 days per week to 2-butoxyethanol at 0, 20, 86, or 245 ppm (Dodd et al. 1983). Animals at the high concentration also exhibited red-stained urine (hematuria) after one or two treatments, which was not observed in the postexposure period of 14 days (Dodd et al. 1983). Hematuria was noted in male Wistar-derived (Alpk/Ap) rats exposed to 800 ppm for 3 hours (Doe 1984), in

2. HEALTH EFFECTS

nonpregnant female Sprague-Dawley rats exposed to 250 ppm 2-butoxyethanol for up to 7 hours, and on the first exposure day in pregnant Sprague-Dawley rats exposed to 150 and 200 ppm for 7 hours per day on gestational days 7-15 (Nelson et al. 1984). Timed-pregnant Fischer 344 rats exposed by inhalation to 2-butoxyethanol vapor at concentrations of 0, 25, 50, 100, or 200 ppm for 6 hours per day on gestational days 6-15 exhibited hematuria at 100 and 200 ppm (Tyl et al. 1984). In the same study, red fluid on the tray paper, possibly evidence of hematuria, was observed in timed-pregnant New Zealand rabbits exposed to 100 and 200 ppm 6 hours per day during gestation. Male albino rabbits exposed to approximately 400 ppm 2-butoxyethanol for 1-2 days at 7 hours per day exhibited darkened kidneys and hematuria (Dow 1986).

Cloudy swelling of the convoluted tubules was observed in female rats exposed to 432 ppm 2-butoxyethanol for 2 hours (Carpenter et al. 1956). No effect on urine output was seen in male rats exposed to 20 or 100 ppm 2-butoxyethanol for 12 days (Johanson 1994), or on kidney weight in pregnant rabbits exposed to doses up to 200 ppm during gestation (Tyl et al. 1984). In a study in which Swiss mice were exposed to 390-1,210 ppm 2-butoxyethanol for 7 hours, interstitial nephritis was reported (Werner et al. 1943a). The concentrations at which nephritis was observed were not stated. Gross lesions in the kidneys were not observed in guinea pigs exposed to 2-butoxyethanol for 1 hour followed by a 14-day observation period at 661 ppm for females and 633 ppm for males (Nacbreiner 1994). One female dog, exposed repeatedly to 617 ppm 2-butoxyethanol for a total of 13.5 hours over 2 days exhibited congestion of the kidneys upon necropsy (Carpenter et al. 1956). Similar results were obtained in a female dog that died after exposure to 385 ppm 2-butoxyethanol for 8 days (Carpenter et al. 1956). The effect was not observed in the male dog that died after exposure to the same concentration for 28 days. This study is limited in that only one female dog was exposed to concentrations of 385 or 617 ppm, and only one male was used in the 385 ppm exposure concentration group.

Renal effects have also been observed in animals exposed to 2-butoxyethanol in intermediate-duration studies. Statistically significant increases in kidney weight were observed in Sherman rats exposed to ≥ 107 ppm and in guinea pigs exposed to ≥ 203 ppm for 7 hours per day, 5 days per week for 30 days (Carpenter et al. 1956). Cloudy swelling of the convoluted and loop tubules was observed upon necropsy of the guinea pigs that died at 376 and 494 ppm. No effect on kidney weight and no gross renal lesions were found in mice exposed to ≤ 400 ppm for 7 hours per day for 30-90 days. No blood or urinalysis parameters were affected, and no gross or histologically observed lesions in the kidneys or urinary bladder were found in Fischer 344 rats exposed to ≤ 77 ppm for 7 hours per day, 5 days per week for 13 weeks (Dodd et al. 1983).

2. HEALTH EFFECTS

Gross or histopathological changes in the kidneys were not observed in two dogs exposed to 415 ppm 2-butoxyethanol 17 hours per day, 5 days per week for 12 weeks (Werner et al. 1943b).

In a study of 2-butoxyethanol acetate, Wistar rats and New Zealand white rabbits were exposed to a saturated vapor-air mixture of approximately 400 ppm 2-butoxyethanol acetate for 4 hours, and then observed for 14 days after exposure (Truhaut et al. 1979). No blood was found in the urine of rats, although rabbits exhibited transient and slight hematuria. When the animals were sacrificed at the end of 2 weeks, no gross pathological lesions were observed in the renal system of either rats or rabbits. In the same study, renal effects were noted in both rats and rabbits after intermittent exposure (5 days per week, 4 hours per day) to 400 ppm 2-butoxyethanol acetate for 1 month (Truhaut et al. 1979). Hematuria and tubular nephrosis, ranging from cellular cloudy swelling to hemorrhagic necrosis, were noted in female rats sacrificed at the end of the exposure period, but not in those sacrificed 1 week after exposure ceased. Rabbits exposed for 1 month exhibited hypertrophic kidneys filled with blood and blood-filled bladders (hematuria) at death during week 4. These rabbits, and those surviving to the end of the exposure period, exhibited necrotizing tubular nephrosis, atrophic tubular dilation, and luminal granular deposits. Effects observed in rabbits exposed to 100 ppm 2-butoxyethanol acetate for 10 months, 5 days per week, 4 hours per day included tubular nephritis with tubular enlargement, cortical atrophy, inflammatory fibrosis, and tubular Henle's loop dilation. Effects in rats exposed to the same concentration for 10 months were described as similar to those observed in rabbits, but the lesions were more discrete and inconstant (i.e., not always present) and were characterized (only in males) by tubular enlargement and atrophy, nephritis, inflammatory fibrosis, dilatation of Henle's loop and the distal convoluted tubules, and hyaline casts (Truhaut et al. 1979).

Endocrine Effects. Severely hemorrhaged adrenal glands were observed at necropsy in a female dog that died after exposure to 385 ppm 2-butoxyethanol for 8 days (Carpenter et al. 1956). No gross or histologically observed lesions were found in the adrenal, parathyroid, thyroid, or pituitary in Fischer 344 rats exposed to ≤ 77 ppm, 6 hours per day, 5 days per week for 13 weeks (Dodd et al. 1983). Gross lesions in the pituitary, thyroid gland, pancreas, parathyroid gland, and adrenal glands were not observed in guinea pigs exposed to 2-butoxyethanol for 1 hour followed by a 14-day observation period at 661 ppm for females and 633 ppm for males (Nachreiner 1994).

In a study of 2-butoxyethanol acetate, Wistar rats and New Zealand white rabbits were exposed to 400 ppm 2-butoxyethanol acetate for 4 hours, followed by a 14-day observation period (Truhaut et al. 1979). When the animals were sacrificed at the end of 2 weeks, no gross pathological lesions were observed in the adrenal

2. HEALTH EFFECTS

gland or pancreas of either rats or rabbits. Similarly, no gross or histologically observed lesions were noted in the pancreas or adrenal glands of rats and rabbits exposed for 4 hours per day, 5 days per week to 400 ppm of 2-butoxyethanol acetate for 1 month or to 100 ppm for 10 months (Truhaut et al. 1979).

Dermal Effects. Nonpregnant female rats exposed to 2-butoxyethanol at concentrations of 250-500 ppm for up to 7 hours exhibited necrosis of the tail tip 1 week after exposure (Nelson et al. 1984). In addition, pregnant Fischer 344 rats exposed to 200 ppm 2-butoxyethanol for 6 hours per day during gestational days 6-15 exhibited necrosis of the tail tip (Tyl et al. 1984). The cause of necrosis of the tail tip was not clearly stated, but possibly it is associated with the effects of 2-butoxyethanol on the red blood cells, and subsequent vascular response. Stained fur was noted in both pregnant Fischer 344 rats dosed during gestational days 6-15 and pregnant New Zealand white rabbits exposed on gestational days 6-18 to 200 ppm 2-butoxyethanol for 6 hours per day (Tyl et al. 1984). The exact cause of the stained fur was not noted.

Ocular Effects. Male and female volunteers exposed to 98, 113, or 195 ppm 2-butoxyethanol for 4-8 hours experienced ocular irritation during exposure to 113 and 195 ppm (Carpenter et al. 1956).

Pregnant Fischer 344 rats exposed to 25-200 ppm during gestational days 6-15 exhibited periocular wetness at all concentrations, whereas New Zealand white rabbits exposed to 100 and 200 ppm, but not 25 ppm, 2-butoxyethanol during gestation exhibited the same effect (Tyl et al. 1984). The ocular irritation in the human subjects and the periocular wetness in the animals were probably due to direct contact of the eyes with the 2-butoxyethanol vapor; these effects are also discussed in Section 2.2.3.2 for Ocular Effects.

Ocular infections were observed in a female dog that died after 8 days and in a male dog that died after 28 days following exposure to 385 ppm 2-butoxyethanol (Carpenter et al. 1956). It is not clear whether the ocular infections were due to 2-butoxyethanol exposure since no controls were included. In another experiment by Carpenter et al. (1956), a male and a female dog exposed to 200 ppm for 31 days showed no effects on the cornea after staining with fluorescein. A slight increase in ocular secretions was observed in 2 dogs exposed to 415 ppm 2-butoxyethanol 17 hours per day, 5 days per week for 12 weeks (Werner et al. 1943b). In male albino rabbits exposed to 400-411 ppm for 7 hours per day for 1-2 days, a reddish ocular discharge accompanied by yellow discoloration of the sclera was observed upon necropsy (Dow 1986). These effects may have been secondary to the hemolytic property of 2-butoxyethanol.

2. HEALTH EFFECTS

Ophthalmological examination of the eyes revealed no ocular effects in Fischer 344 rats exposed 5 days per week, 6 hours per day to ≤ 245 ppm 2-butoxyethanol for 9 days or to ≤ 77 ppm for 13 weeks (Dodd et al. 1983).

Body Weight Effects. Fischer 344 rats exposed for 4 hours to concentrations of 0, 202, 523, and 867 ppm 2-butoxyethanol exhibited significant weight loss on the first day after exposure at concentrations ≥ 523 ppm 2-butoxyethanol, but weight gain resumed 4 days postexposure; body weight returned to preexposure values between days 7-14, and continued to increase for the duration of the 14-day observation period (Dodd et al. 1983). Similarly, decreased weight gain was observed when male rats were exposed to 245 ppm or female rats were exposed to 86 ppm for 9 days (Dodd et al. 1983), although no effect on body weight was observed in male Sprague-Dawley rats exposed to 57-58 ppm for 7 hours per day for 4 days (Dow 1972) or to 100 ppm 2-butoxyethanol for 12 days, 24 hours per day (Johanson 1994). However, after timed-pregnant Fischer 344 rats were exposed to 2-butoxyethanol vapors by inhalation on gestational days 6-15 and New Zealand white rabbits were exposed on gestational days 6-18 to concentrations of 0, 25, 50, 100, or 200 ppm for 6 hours per day, reduced final body weight or reduced weight gain were observed at 100 and 200 ppm in rats and at 200 ppm in rabbits (Tyl et al. 1984). It should be noted that the pregnant rats, but not the pregnant rabbits, had reduced food consumption at 100 ppm and reduced water consumption at 200 ppm, as discussed in Other Systemic Effects below. An unspecified weight loss was found in a female dog that died after exposure for 8 days and in a male dog that died after exposure for 28 days to 385 ppm; anorexia was observed in the female dog (Carpenter et al. 1956). However, no effects on body weight were found in two male dogs exposed to 400-411 ppm, 7 hours per day for 1-5 days (Dow 1986).

No effect on body weight was observed in male and female guinea pigs exposed to 633 ppm or 691 ppm 2-butoxyethanol, respectively, for 1 hour (Nachreiner 1944). No effect on body weight was observed in male and female Sherman rats exposed to ≤ 203 ppm 2-butoxyethanol or in guinea pigs exposed to ≤ 495 ppm for 7 hours per day, 5 days per week, for 30 days (Carpenter et al. 1956). However, in mice exposed for 30, 60, or 90 days, a significant but unspecified decrease in body weight was noted after the 60-day exposure at 400 ppm. Two dogs exposed to 415 ppm 2-butoxyethanol 17 hours per day, 5 days per week, for 12 weeks gradually lost 6-9% of their body weight (Werner et al. 1943b). No control body weight data were provided, although the study authors indicated that the other dogs in the study gained weight or remained constant throughout the study period. In an intermediate-duration study in male and female Fischer 344 rats, female rats exposed to 77 ppm 2-butoxyethanol for 13 weeks, 5 days per week, 6 hours per day showed a transient

2. HEALTH EFFECTS

unspecified decrease in body weight gain during exposure weeks 24 that was not evident at necropsy (Dodd et al. 1983).

No effects on body weight were noted in Wistar rats or New Zealand white rabbits exposed intermittently (5 days per week, 4 hours per day) to 400 ppm 2-butoxyethanol acetate for 1 month or to 100 ppm 2-butoxyethanol acetate for 10 months (Truhaut et al. 1979).

Other Systemic Effects. No effect on food or water intake was observed for male Sprague-Dawley rats exposed to 20 or 100 ppm 2-butoxyethanol for 24 hours per day for 12 days (Johanson 1994).

Timed-pregnant Fischer 344 rats exposed to 2-butoxyethanol vapors by inhalation on gestational days 6-15 at concentrations of 0, 25, 50, 100, or 200 ppm for 6 hours per day exhibited reduced food consumption at 100 ppm and reduced water consumption at 200 ppm (Tyl et al. 1984). No effect on food or water consumption was observed for rabbits exposed by the same regimen on gestational days 6-18 (Tyl et al. 1984). Several investigators note red staining or red fluid on cage papers or in the cages but do not further identify this observation (Tyl et al. 1984). Based on the observations of hematuria and hemoglobinuria by other investigators, it seems likely that observations of red stains or fluid represent hematuria or hemoglobinuria. No adverse changes were noted with respect to general appearance and appetite after exposure of guinea pigs and dogs to concentrations ≤ 58 ppm 2-butoxyethanol for 4 days, 7 hours per day (Dow 1972) or after exposure of guinea pigs to 400-411 ppm for 1-5 days, 7 hours per day (Dow 1986).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after inhalation exposure to 2-butoxyethanol or 2-butoxyethanol acetate. No studies were located regarding immunological effects in animals after inhalation exposure to 2-butoxyethanol or 2-butoxyethanol acetate. However, studies in animals that examined effects on lymphoreticular organs were located.

In a study in which Swiss mice were exposed to 390-1,210 ppm 2-butoxyethanol for 7 hours, focal necrosis and lymphoid hyperplasia in the spleen were observed (Werner et al. 1943a). The concentrations at which these effects occurred were not stated. Timed-pregnant Fischer 344 rats exposed to 0, 25, 50, 100, or 200 ppm 2-butoxyethanol by inhalation for 6 hours per day on gestational days 6-15 exhibited increased spleen weights at 200 ppm; pregnant New Zealand white rabbits exposed to the same concentrations for a comparable period during gestation (gestational days 6-18) showed no effect on spleen weight (Tyl et al.

2. HEALTH EFFECTS

1984). No histological examination of the spleen was performed. Gross examination did not reveal any effects in the spleen, thymic region, or lymph nodes in guinea pigs exposed to 2-butoxyethanol for 1 hour followed by a 14-day observation period at 633 ppm for males and 691 ppm for females (Nachreiner 1994). Histological examination of the spleen, mediastinal lymph nodes, and thymus revealed no pathological lesions in Fischer 344 rats exposed intermittently to <77 ppm for 13 weeks (Dodd et al. 1983). Histological examination did not reveal any effects in the spleen of 2 dogs exposed to 415 ppm 2-butoxyethanol 17 hours per day, 5 days per week for 12 weeks (Werner et al. 1943b).

In a study of 2-butoxyethanol acetate, Wistar rats and New Zealand white rabbits were exposed to 400 ppm 2-butoxyethanol acetate for 4 hours and then observed for 14 days after exposure (Truhaut et al. 1979). When the animals were sacrificed at the end of 2 weeks, no gross pathological lesions were observed in the spleen of either rats or rabbits. Similarly, no gross or histologically observed lesions were found in the spleens after rats and rabbits were exposed intermittently to 400 ppm of 2-butoxyethanol acetate for 1 month or to 100 ppm for 10 months (Truhaut et al. 1979).

Spleen weight effects may be due to hemolysis, which is discussed under Hematological Effects. Refer to Section 2.4.2 Mechanisms of Toxicity for information on how this effect may occur.

The highest NOAEL values and all LOAEL values from each reliable study for lymphoreticular effects in each species and duration category are recorded in Tables 2-1 and 2-2 and plotted in Figures 2-1 and 2-2.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans after inhalation exposure to 2-butoxyethanol acetate. Male and female volunteers exposed to 98, 113, or 195 ppm 2-butoxyethanol for 4-8 hours experienced headache at 98 ppm and disturbed taste sensation at 113 and 195 ppm (Carpenter et al. 1956).

Male and female Fischer 344 rats experienced loss of coordination after exposure to 523 and 867 ppm 2-butoxyethanol, but not to 202 ppm, for 4 hours (Dodd et al. 1983). Extreme physical weakness was observed in a female dog exposed to 617 ppm for 13.5 hours over 2 days, and weakness and apathy were observed in other dogs that died after exposure to 385 ppm for 8 days (one female) and 28 days (one male) (Carpenter et al. 1956). An additional study of two male beagles exposed to approximately 400 ppm 2-butoxyethanol for 7 hours per day for up to 5 days showed excess salivation; no adverse effects on

2. HEALTH EFFECTS

demeanor were observed at this or lower concentrations (Dow 1972, 1986). Male albino rabbits exhibited poor coordination of the extremities and loss of equilibrium after exposure to approximately 400 ppm 2-butoxyethanol for 7 hours per day for 1-2 days (Dow 1986). Histological examination of the brain and sciatic nerve revealed no pathological lesions in Fischer 344 rats exposed to ≤ 77 ppm intermittently for 13 weeks (Dodd et al. 1983).

Wistar rats and New Zealand white rabbits exposed to 400 ppm 2-butoxyethanol acetate for 4 hours and then observed for 14 days after exposure showed no clinical signs of neurological effects (Truhaut et al. 1979). When the animals were sacrificed at the end of 2 weeks, no gross pathological lesions were observed in the brain of either rats or rabbits. Similarly, no clinical neurological effects and no gross or histologically observed lesions in brain were noted when rats and rabbits were exposed intermittently to 400 ppm of 2-butoxyethanol acetate for 1 month or to 100 ppm for 10 months (Truhaut et al. 1979).

The highest NOAEL values and all LOAJZL values from each reliable study for neurological effects in each species and duration category are recorded in Tables 2-1 and 2-2 and plotted in Figures 2-1 and 2-2.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to 2-butoxyethanol or 2-butoxyethanol acetate.

Male Alpk/Ap (Wistar-derived) rats were exposed to 800 ppm 2-butoxyethanol for 3 hours (Doe 1984). The rats were then observed during exposure and throughout a subsequent 14-day observation period. On the 15th day, animals were killed and gross macroscopic examination was conducted. No effect on testicular weight was observed. Effects on testicular weight were not noted in Fischer 344 rats exposed to ≤ 867 ppm for 4 hours, to ≤ 245 ppm intermittently for 9 days, or to ≤ 77 ppm intermittently for 13 weeks (Dodd et al. 1983); histological examination of the epididymides and testes of male rats in a 13-week study revealed no pathological lesions. Reproductive organs of the female rats in the 13-week study by Dodd et al. (1983) were not examined histologically. Gross changes in male (testes, penis, seminal vesicle, epididymides, prostate) and female (ovaries, uterus, cervix, vagina, vulva) reproductive organs were not observed in guinea pigs exposed to 2-butoxyethanol for 1 hour at 633 ppm for males and 691 ppm for females, followed by a 14-day observation period (Nachreiner 1994).

2. HEALTH EFFECTS

Pregnant Fischer 344 rats exposed intermittently to 25-200 ppm 2-butoxyethanol during gestational days 6-15 exhibited reduced maternal gravid uterine weight, a 50% decrease in viable implants and in live fetuses per litter, and an eight-fold increase in non-viable implants at 200 ppm, but not at the lower concentrations (Tyl et al. 1984). New Zealand white rabbits similarly exposed to the same concentrations on gestational days 6-18 also exhibited decreases in total implants and implant viability at 200 ppm (Tyl et al. 1984). The exposure concentrations that resulted in reproductive effects following exposure of rats and rabbits to 2-butoxyethanol during gestation also resulted in maternal toxicity (see Section 2.2.1.2).

Wistar rats and New Zealand white rabbits exposed to 400 ppm 2-butoxyethanol acetate for 4 hours, and then observed for 14 days after exposure, showed no signs of vaginal bleeding or testicular shrinkage (Truhaut et al. 1979). When the animals were sacrificed at the end of 2 weeks, no gross pathological lesions were observed in the testes or ovaries of either rats or rabbits exposed for 4 hours to 400 ppm 2-butoxyethanol acetate. Similarly, no gross or histologically observed lesions in the testes or ovaries were seen when rats and rabbits were exposed intermittently to 400 ppm of 2-butoxyethanol acetate for 1 month or to 100 ppm for 10 months (Truhaut et al. 1979).

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Tables 2-1 and 2-2 and plotted in Figures 2-1 and 2-2.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to 2-butoxyethanol or 2-butoxyethanol acetate. No studies were located regarding developmental effects in animals after inhalation exposure to 2-butoxyethanol acetate.

2-Butoxyethanol was vaporized and administered at concentrations of 0, 150, or 200 ppm to pregnant rats for 7 hours per day on gestational days 7-15 (Nelson et al. 1984). On day 20, the females were weighed and euthanized. The entire uterus was removed and the numbers of resorption sites and live fetuses were determined. Fetuses were serially removed, weighed, and examined for visceral malformations and skeletal defects. No developmental effects were noted. In a similar study, timed-pregnant Fischer 344 rats were exposed to 2-butoxyethanol vapors by inhalation on gestational days 6-15 at concentrations of 0, 25, 50, 100, or 200 ppm for 6 hours per day (Tyl et al. 1984). Fetuses were weighed and sexed, and evaluated for viability, body weight, and morphological development, including external, visceral, and skeletal

2. HEALTH EFFECTS

malformations. Fetotoxicity, observed as retarded skeletal ossification of vertebral arches or centra, sternebrae, or phalanges, was observed at 100 and 200 ppm, concentrations that resulted in maternal toxicity. For pregnant New Zealand white rabbits similarly exposed to the same concentrations on gestational days 6-18, fetal skeletal ossification of sternebrae and rudimentary rib was also delayed at 200 ppm but not at ≤ 100 ppm (Tyl et al. 1984). Gravid uterine weight was reduced and maternal toxicity was observed at 200 ppm in rabbits (Tyl et al. 1984).

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species in the acute-duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

No increases in micronuclei or sister chromatid exchanges were observed in varnish production workers exposed to both 2-ethoxyethanol and 2-butoxyethanol (Sohnllein et al. 1993). The concentration of 2-ethoxyethanol in the air of the workroom ranged from <0.1 -15.2 ppm, while the range for 2-butoxyethanol was <0.1 -1.4 ppm. Postshift biological monitoring for the acetic acids in urine indicated that urinary levels of 2-ethoxyacetic acid (53.8 mg/L) were higher than urinary levels of 2-butoxyacetic acid (16.4 mg/L). No studies were located regarding genotoxic effects in animals after inhalation exposure to 2-butoxyethanol or 2-butoxyethanol acetate. *In vitro* genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after inhalation exposure to 2-butoxyethanol or 2-butoxyethanol acetate.

2.2.2 Oral Exposure

Oral exposure to 2-butoxyethanol or 2-butoxyethanol acetate may occur through accidental ingestion of contaminated food, water, or commercial products, or from intentional ingestion of commercial products containing these chemicals. Studies describing human oral exposure, in addition to experimental animal studies, are discussed in this section (Section 2.2.2) and have been summarized in several publications (Browning and Curry 1994; EPA 1984; NIOSH 11990; Tyler 1984).

2. HEALTH EFFECTS

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to 2-butoxyethanol acetate, or death in humans or animals after oral exposure to the major metabolite, 2-butoxyacetic acid.

An 87-year-old woman died after ingesting an unknown amount of disinfectant cleaner containing 6.5% 2-butoxyethanol (Litovitz et al. 1991). The other ingredients in the cleaner were not stated. Upon admission to the hospital the blood ethylene glycol level was 100 mg/dL. Complications included prolonged metabolic acidosis, hypotension, ventricular arrhythmias, hepatic and renal failure, and disseminated intravascular coagulation. Although the blood ethylene glycol level decreased to 10 mg/dL, she had a cardiac arrest and died 3 days after admission.

Acute oral LD₅₀ (lethal dose, 50% kill) values of 2-butoxyethanol for rats ranged from 530 to 3,000 mg/kg (Carpenter et al. 1956; Eastman Kodak 1988; Nelson et al. 1984; Olin 1976; Smyth et al. 1941; Union Carbide 1980b). In rats of an unspecified strain given 2-butoxyethanol by gavage in water, death occurred in three of five rats at 500 mg/kg and two of two rats at 1,000 mg/kg (Dow 1959). No deaths occurred at 252 mg/kg. In female Fischer 344 rats, deaths occurred in two of three rats at 2,000 mg/kg, while no deaths occurred at ≤ 1,000 mg/kg (Dow 1981). In contrast, when male Fischer 344 rats were given 50, 100, 200, or 400 mg/kg/day for 2 days, one of six rats died and another was moribund at 200 mg/kg/day; six of six rats died at 400 mg/kg/day; no rats died at ≤ 100 mg/kg/day (Smialowicz et al. 1992). When female Sprague-Dawley female rats were treated with a single gavage dose of 1,500 mg/kg 2-butoxyethanol in water, 75% died (Sivarao and Mehendale 1995). When rats were treated with a non-lethal dose (500 mg/kg) followed 7 days later by a dose of 1,500 mg/kg, only 13% died. No male Fischer 344 rats given 126 mg/kg 2-butoxyethanol in water by gavage died (Corley et al. 1994). Pregnant Fischer 344 rats dosed on gestational days 9-11 or 11-13 with doses of 150, 300, or 600 mg/kg/day in a preliminary dose range-finding study exhibited 11% (1 of 9) and 17% (1 of 6) mortality within the first 24 hours at doses of 300 and 150 mg/kg/day, respectively (NTP 1989). Two of 6 of the pregnant rats treated on gestational days 9-11 and 1 of 7 pregnant rats treated on gestational days 11-13 died at 600 mg/kg/day dose level. However, no mortality was observed in the definitive study with doses ≤ 200 mg/kg/day on gestational days 9-11 and ≤ 300 mg/kg/day on gestational days 11-13 (NTP 1989). Similarly, no deaths occurred in male or female Fischer 344/N rats dosed with ≤ 346 mg/kg/day or ≤ 265 mg/kg/day, respectively, in drinking water for 2 weeks (NTP 1993). However, in male COBS CD (SD)BR rats given doses of 222, 443, or 885 mg/kg/day for 5 days per week for

2. HEALTH EFFECTS

23 days, death occurred in 1 of 10 on day 13 at 443 mg/kg/day, and in 1 of 10 on day 13, and 1 of 9 on day 23 at 885 mg/kg/day (Eastman Kodak 1983; Krasavage 1986).

Acute oral LD₅₀ values for mice were reported to be 1,230 mg/kg (Carpenter et al. 1956) and 1,519 mg/kg (Eastman Kodak 1988). When time-mated CD-1 mice were treated by gavage on gestational days 6-13 with 1,180 mg/kg/day 2-butoxyethanol, death occurred in 4 of 35 pregnant mice and 6 of 15 nonpregnant mice (Hardin et al. 1987; Schuler et al. 1984). In a similar study in mated CD-1 mice given 0, 350, 650, 1,000, 1,500, or 2,000 mg/kg 2-butoxyethanol by gavage on gestational days 8-14, three of six died at 1,500 mg/kg/day and six of six died at 2,000 mg/kg/day (Wier et al. 1987). In Swiss CD-1 mice given 2-butoxyethanol in drinking water at doses ≤ 12,750 mg/kg/day for 2 weeks, deaths were observed in two of eight males and five of eight females at 12,750 mg/kg/day (Heindel et al. 1990). None of the mice died at doses ≤ 6,375 mg/kg/day. No deaths were observed in B6C3F₁ mice dosed with ≤ 627 mg/kg/day for males or ≤ 1,364 mg/kg/day for females in drinking water for 2 weeks (NTP 1993).

Acute oral LD₅₀ values for other species were reported to be 1,200 (Carpenter et al. 1956; Smyth et al. 1941) and 1,414 mg/kg (Shepard 1994b) for guinea pigs and 320-370 mg/kg for rabbits (Carpenter et al. 1956).

In intermediate-duration studies of 2-butoxyethanol, no deaths occurred in male or female Sherman rats dosed with ≤ 1540 mg/kg/day in the diet for 90 days (Carpenter et al. 1956), in Fischer 344/N rats dosed with ≤ 452 mg/kg/day for males and ≤ 470 mg/kg/day for females in drinking water for 13 weeks (NTP 1993), in male Fischer 344/N rats dosed with ≤ 443 mg/kg/day in drinking water for 60 days (NTP 1993), or in an unspecified strain of rats dosed with ≤ 976 mg/kg/day in the diet for 91-93 days (Weil and Carpenter 1963). Similarly, no deaths occurred in B6C3F₁ mice dosed with ≤ 694 mg/kg/day (males) or ≤ 1,306 mg/kg/day (females) for 13 weeks (NTP 1993). However, in Swiss CD-1 mice given 0, 700, 1,300, or 2,000 mg/kg/day in drinking water for 21 weeks, deaths occurred in 1 of 20 females at 700 mg/kg/day, 6 of 20 females at 1,300 mg/kg/day, and 13 of 20 females at 2,000 mg/kg/day (Heindel et al. 1990). None of the male mice died. In addition, deaths occurred in five of five male JCL-ICR mice dosed with 2,000 mg/kg/day by gavage 5 days per week for 5 weeks (Nagano et al. 1979, 1984). No deaths occurred in the mice given lower doses (≤ 1,000 mg/kg/day).

Mortality data for 2-butoxyethanol acetate are limited to LD₅₀ values. In Wistar rats given an oral dose of 2-butoxyethanol acetate in olive oil by gastric intubation, the LD₅₀ values were determined to be 3,000 mg/kg for males and 2,400 mg/kg for females (Truhaut et al. 1979).

2. HEALTH EFFECTS

The LD₅₀ values and all LOAEL values from each reliable study for death in each species and duration category are recorded in Tables 2-3 and 2-4 and plotted in Figures 2-3 and 2-4.

2.2.2.2 Systemic Effects

No studies were located regarding gastrointestinal, musculoskeletal, endocrine, dermal, or body weight effects in humans, or metabolic effects in animals following oral exposure to 2-butoxyethanol. No reliable studies were located describing systemic effects in humans or animals following oral exposure to 2-butoxyethanol acetate. One study, Truhaut et al. (1979), gives some data for oral exposure regarding respiratory, cardiovascular, hematological, hepatic, renal, and endocrine effects, but does not specify the doses given. The data from that study have been included in this section for reference. Only one study (Foster et al. 1987) described systemic effects of 2-butoxyacetic acid after oral exposure in animals, consisting of hepatic, renal, and body weight effects. Available data pertaining to systemic effects of all three compounds are presented below.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Tables 2-3 and 2-5 and plotted in Figures 2-3 and 2-5.

Respiratory Effects. A male patient who was an abuser of alcohol and had a history of trichloroethylene ingestion was admitted to the hospital after ingestion of 500 mL of a household cleaning fluid, Glassex (Bauer et al. 1992). The concentration of 2-butoxyethanol as determined by gas-chromatography was 9.1% (45.5 g), equivalent to a dose of 650 mg/kg. Diffuse pulmonary edema was noted. In another case report, a woman was admitted to the hospital after ingesting 250-500 mL window cleaner containing 12% 2-butoxyethanol (Rambourg-Schepens et al. 1988). The estimated dose was 467-933 mg/kg. The woman was ventilating poorly and required a respirator for 5 days after admittance. Similarly, a woman who ingested 25-30 g (391-469 mg/kg) 2-butoxyethanol contained in a window cleaning agent exhibited obstructive respiration and was placed on a respirator upon admission to the hospital (Gijssenbergh et al. 1989). However, two children who accidentally ingested a window cleaning agent containing 3 or 24 mL 2-butoxyethanol (270 or 1,862 mg/kg 2-butoxyethanol) showed no respiratory effects (Dean and Krenzelok 1992). Gastric emptying by administration of syrup of ipecac or by gastric lavage within minutes or hours of ingestion (time not specified) may have prevented any adverse effects.

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral

Key to figure ^a	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Rat (Wistar, Sherman, Carworth- Wistar)	once (G)				530- 3000 (LD ₅₀)	Carpenter et al. 1956
2	Rat (NS)	NS (GW)				500 (death in 3/5 animals)	Dow 1959
3	Rat (Fischer- 344)	once (G)				2000 F (2/3 died)	Dow 1981
4	Rat (CrI:COBS CD (SD)BR)	13 d 5 d/wk (G)				443 M (death in 1/10)	Eastman Kodak 1983; Krasavage 1986
5	Rat (CD)	NS (G)				1746 M (LD ₅₀)	Eastman Kodak 1988
6	Rat (NS)	NS				1480 (LD ₅₀)	Nelson et al. 1984
7	Rat (Fischer- 344)	Gd 11-13 (GW)				150 F (1/9 died 24 hrs after exposure)	NTP 1989

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
8	Rat (Wistar)	once (G)				1590 M (LD ₅₀)	Olin 1976
9	Rat (Fischer- 344)	2 d (GW)				200 M (death in 1/6)	Smialowicz et al. 1992
10	Rat (Wistar)	once (GW)				1480 M (LD ₅₀)	Smyth et al. 1941
11	Rat (Wistar)	once (G)				2417 (LD ₅₀)	Union Carbide 1980b
12	Mouse (NS)	once				1230 M (LD ₅₀)	Carpenter et al. 1956
13	Mouse (Charles River, COBS, CD-1)	NS (G)				1519 M (LD ₅₀)	Eastman Kodak 1988
14	Mouse (CD-1)	Gd 6-13 (GW)				1180 F (death in 4/35 pregnant mice and 6/15 nonpregnant mice)	Hardin et al. 1987; Schuler et al. 1984
15	Mouse (Swiss CD-1)	2 wk (W)				12750 (death in 2/8 males, 5/8 females)	Heindel et al. 1990

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
16	Mouse (CD-1)	Gd 8-14 1x/d (G)				1500 F (death in 3/6)	Wier et al. 1987
17	Gn Pig (NS)	once (G)				1200 (LD ₅₀)	Carpenter et al. 1956
18	Gn Pig (Hartley)	once (GW)				1414 (LD ₅₀)	Shepard 1994b
19	Rabbit (NS)	once				320-370 M (LD ₅₀)	Carpenter et al. 1956
Systemic							
20	Human	once (IN)	Resp Cardio Hemato Hepatic Renal Metab		650M (slight albuminuria)	650 M (diffuse pulmonary edema) 650 M (hypotension, tachycardia, sinusal rhythm) 650 M (low prothrombin time, nonhemolytic anemia, thrombopenia) 650 M (abnormal liver function) 650 M (metabolic acidosis and hypoxemia with lactic acidosis)	Bauer et al. 1992

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
21	Human	once (IN)	Resp			391 F (obstructive respiration)	Gijzenbergh et al. 1989
			Cardio			391 F (low blood pressure)	
			Hemato			391 F (decreased hemoglobin from 11.9 to 8.9 g/dL)	
			Renal			391 F (hematuria)	
			Ocular			391 F (isocoric light reactive mydriasis)	
			Metab			391 F (marked metabolic acidosis)	
22	Human	2x	Hepatic		1006 M (increased serum ALT, AST, bilirubin; only after first exposure)		Gualtieri et al. 1995
			Metab			1006 M (significant acid-base disturbance)	
23	Human	once (IN)	Resp			467 F (poor ventilation)	Rambourg- Schepens et al. 1988
			Cardio	467 F			
			Hemato			467 F (hemoglobinuria, progressive erythropenia)	
			Hepatic	467 F			
			Renal			467 F (increased serum creatinine, oxaluria)	
			Metab			467 F (metabolic acidosis, hypokalaemia)	

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
24	Rat (Wistar, Sherman, Carworth- Wistar)	once (G)	Resp			530	(congested or hemorrhagic lungs)	Carpenter et al. 1956
			Hemato			3000 M 1500 F	(hemoglobinuria)	
			Hepatic			530	(mottled livers)	
			Renal			530	(severely congested kidneys)	
			Dermal	530	(rough coat)			
25	Rat (Fischer- 344)	once (GW)	Hemato	8.6 M		126 M	(hemolysis, hemoglobinuria)	Corley et al. 1994
26	Rat (NS)	NS (GW)	Renal	1000 F	2000 F	(rapid, shallow breathing)		Dow 1959
			Resp	252		500	(hematuria)	
27	Rat (Fischer- 344)	once (G)	Dermal	500 F	1000 F	(rough hair coats; necrosis of tail)		Dow 1981
			Ocular Bd Wt	1000 F 2000 F	2000 F	(palpebral closure)		
			Other		130 F	(staining in perineal region)		
28	Rat (Fischer- 344)	once (GW)	Hemato			250 M	(hemolysis)	Ghanayem and Sullivan 1993

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
29	Rat (Fischer- 344)	once (GW)	Hemato		32 ^b M (hemoglobinuria)		Ghanayem et al. 1987a
			Hepatic	125 M	250 M (focal coagulative necrosis of hepatocytes, 1/6)		
			Renal		125 M (hemoglobin casts in proximal tubules)		
30	Rat (Fischer- 344)	once (GW)	Hemato		500 M (increase in free hemoglobin in the plasma, hemoglobinuria, hemolysis)		Ghanayem et al. 1987b
			Hepatic		500 M (coagulative necrosis and hemosiderin deposition in hepatocytes and Kupffer cells)		
			Renal		500 M (intracytoplasmic hemoglobin and hemoglobin casts in the proximal tubules)		
31	Rat (Fischer- 344)	once (GW)	Hemato		125 M (increase in free hemoglobin in the plasma, hemoglobinuria, hemolysis)		Ghanayem et al. 1987b
32	Rat (Fischer- 344)	once (GW)	Hemato		125 M (increased HCT, PCV, and MCV followed by decline with hemolysis)		Ghanayem et al. 1990b

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
33	Rat (Fischer- 344)	1-12 d 1x/d (GW)	Hemato			125 M (hemolytic anemia)	Ghanayem et al. 1992
			Hepatic		125M (time-dependent changes in liver weight: declined 10% on days 3 and 6, increased 5% on day 12)		
34	Rat (Fischer- 344)	4 d (GW)	Hemato			500 M (reduction of 23% in RBC, 11% in HGB, increase of 24% in MCV, 600% in reticulocyte counts and 16% in MCH; marrow hyperplasia)	Grant et al. 1985
			Hepatic		500M (15.8% increase in relative liver weights after day 1 recovery)		
			Renal	500 M	1000M (12.4% increase in relative kidney weight after day 1 recovery)		
			Bd Wt	500 M		1000 M (13.4% reduction in body weight gain after day 1 recovery and 26% reduction in body weight gain at day 4 recovery)	

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
35	Rat (Fischer- 344)	Gd 9-11 (GW)	Resp	300 F	600 F (dyspnea)		NTP 1989
			Hemato			150 F (increased reticulocytes, MCV, MCH and platelet count, decreased RBC, HGB, HCT, and MCHC)	
			Hepatic	150 F	300 F (27.1% decreased absolute liver weight [Gd 12])		
			Renal	300 F		600 F (urethral bleeding [hematuria])	
			Dermal	300 F	600 F (pale coloration, not further described)		
			Ocular Bd Wt	300 F	600 F (chromodacryorrhea)	150 F (gestational weight gain decreased 34.7% [Gd 12])	
			Other		150 F (reduced food and water intake)		
		300 F	600 F (dehydration, cold to touch)				

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
36	Rat (Fischer- 344)	Gd 11-13 (GW)	Resp	300 F	600 F (dyspnea)		NTP 1989
			Hemato			150 F (increased reticulocytes, MCV, MCH and platelet count, decreased RBC, HGB, HCT and MCHC)	
			Hepatic	150 F	300 F (11.5% decreased absolute liver weight [Gd 14])		
			Renal	300 F		600 F (urethral bleeding [hematuria])	
			Dermal	300 F	600 F (pale coloration, not further described)		
			Ocular Bd Wt	300 F	600 F (chromodacryorrhea)	150 F (gestational weight gain decreased 28.9% [Gd 14])	
			Other		150 F (reduced food and water intake)		
		300 F	600 F (dehydration, cold to touch)				

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to figure ^a	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
37	Rat (Fischer- 344)	Gd 9-11 (GW)	Hemato	30 F		100 F (reduced RBC, HCT and HGB, increased reticulocytes, WBC, platelet count, MCV and MCH)	NTP 1989
			Hepatic	100 F	200 F (decreased absolute maternal liver weights: 11.1% [Gd 20], 15.5% [Gd 12])		
			Renal Bd Wt	200 F 100 F		200 F (gestational weight gain decreased 35.3% [Gd 20])	
			Other	100 F	200 F (decreased food and water intake)		
38	Rat (Fischer- 344)	Gd 11-13 (GW)	Hemato	30 F		100 F (reduced RBC, HCT and HGB, increased reticulocytes, WBC, platelet count, MCV and MCH)	NTP 1989
			Hepatic	100 F	300 F (decreased 11.8% [Gd 14] absolute maternal liver weights)		
			Renal Bd Wt	300 F 100 F		300 F (gestational weight gain decreased 20.4 % [Gd 20])	
			Other	100 F	300 F (decreased food and water consumption)		

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
39	Rat (F344/N)	2 wk (W)	Resp	346 M 265 F			NTP 1993
			Cardio	346 M 265 F			
			Hepatic	346 M 265 F			
			Renal	346 M 265 F			
			Bd Wt	346 M 203 F		265 F (11% decreased final body weight, 32% decrease in body weight gain)	
			Other	174 M 102 F	242 M (14.1% decreased water consumption) 152 F (16.3% decreased water consumption)		
40	Rat (Wistar)	once (G)	Gastro	1310 M	2560M (very red small intestine)		Olin 1976
			Musc/skel	1310 M	2560M (flaccid)		
			Hepatic	670 M	1310M (very dark liver)		
			Renal	670 M	1310M (dark kidneys in 3/10, enlarged in 4/10)	2560 M (blood in bladder [hematuria])	
			Dermal	670 M	1310M (piloerection)		

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
41	Rat (Wistar)	once (G)	Gastro	1127		2255	(distended stomach, liquid & gas-filled; blood in intestines)	Union Carbide 1980b
			Hepatic	1127	2255	(dark liver)		
			Renal	1127	2255	(red kidneys)		
			Endocr	1127	2255	(red adrenals)		
			Other		1127	(bloody saliva in 1 animal)		
42	Mouse (CD-1)	Gd 6-13 1x/d (GW)	Bd Wt			1180 F	(80% decrease in body weight gain)	Hardin et al. 1987; Schuler et al. 1984
43	Mouse (Swiss CD-1)	2 wk (W)	Bd Wt	6375		12750 M	(31% weight loss)	Heindel et al. 1990
			Other	637	1275	(unspecified decrease in fluid intake)		
44	Mouse (B6C3F1)	2 wk (W)	Resp	627 M 1364 F				NTP 1993
			Cardio	627 M 1364 F				
			Hepatic	627 M 1367 F				
			Renal	627 M 1364 F				
			Bd Wt	627 M 1364 F				
			Other	210 M	370 M (dehydration in 3/5) 150 F (26.5% decreased water consumption)			

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
45	Mouse (CD-1)	Gd 8-14 (G)	Resp	1000 F	1500 F (abnormal breathing)		Wier et al. 1987
			Bd Wt	1500 F	2000 F (unspecified decrease in maternal weight gain)		
46	Mouse (CD-1)	Gd 8-14 1x/d (G)	Bd Wt	650 F	1000 F (unspecified decrease in maternal weight gain)		Wier et al. 1987
47	Gn Pig (Hartley)	once (GW)	Hemato	250 M			Ghanayem and Sullivan 1993
48	Gn Pig (Hartley)	once (GW)	Gastro	500	1000 (moderate to mild necrosis and hemorrhage of the gastric mucosa in 1/5 males and 1/5 females)		Shepard 1994b
			Bd Wt	1000			
Immunological/Lymphoreticular							
49	Rat (Fischer- 344)	once (GW)		63 M	125M (significant increase (110-150%) in relative spleen weight)		Ghanayem et al. 1987a
50	Rat (Fischer- 344)	once (GW)			500M (>220% increase in relative spleen weight due to trapped RBCs)		Ghanayem et al. 1987b

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
51	Rat (Fischer- 344)	once (GW)			125M (relative spleen weight 145-170% of control)		Ghanayem et al. 1987b
52	Rat (Fischer- 344)	1-12 d 1x/d (GW)			125M (increase of about 62% in spleen weight after 6 days, decline of about 45% during days 6-12)		Ghanayem et al. 1992
53	Rat (Fischer- 344)	4 d (GW)			500M (87% increase in relative spleen weight on day 1, extramedullary hematopoiesis)		Grant et al. 1985
54	Rat (Fischer- 344)	Gd 9-11 (GW)			150 F (increased absolute spleen weight [13.5% Gd 20; 54.8% Gd 12])		NTP 1989
55	Rat (Fischer- 344)	Gd 11-13 (GW)			150 F (increased absolute spleen weights [27.1% Gd 20; 67.7% Gd 14])		NTP 1989
56	Rat (Fischer- 344)	Gd 9-11 (GW)		30 F	100 F (increased absolute spleen weight [11.8% Gd 20; 43.9% Gd 12])		NTP 1989
57	Rat (Fischer- 344)	Gd 11-13 (GW)		30 F	100 F (increased absolute spleen weight [17.5% Gd 20; 44.4% Gd 14])		NTP 1989

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
58	Mouse (B6C3F1)	2 wk (W)		210 M 1364 F	370M (decreased 38.3% absolute thymus weight, 38.9% relative thymus weight)	NTP 1993
Neurological						
59	Human	once (IN)				391 F (coma) Gijzenbergh et al. 1989
60	Human	once (IN)				467 F (coma) Rambourg- Schepens et al. 1988
61	Rat (Wistar, Sherman, Carworth- Wistar)	once				530 (sluggishness, prostration, narcosis) Carpenter et al. 1956
62	Rat (NS)	NS (GW)			252 (drowsiness)	Dow 1959
63	Rat (Fischer- 344)	once (G)		1000 F	2000 F (lethargy)	Dow 1981
64	Rat (Cr:COBS CD (SD)BR)	1-3 d (G)		222 M	443M (lethargy after 1st dose)	Eastman Kodak 1983; Krasavage 1986

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to figure ^a	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		Serious (mg/kg/day)
65	Rat (Fischer- 344)	Gd 9-11 (GW)		300 F	600 F (lethargy)	NTP 1989	
66	Rat (Fischer- 344)	Gd 11-13 (GW)		300 F	600 F (lethargy)	NTP 1989	
67	Rat (Wistar)	once (G)		670 M	1310M (lethargy, piloerection)	Olin 1976	
68	Rat (Sprague- Dawley)	once (GW)			500 F (ataxia, piloerection)	Sivarao and Mehendale 1995	
69	Rat (Wistar)	once (G)		1127	2255 (sluggish, unsteady gait)	Union Carbide 1980b	
70	Mouse (CD-1)	Gd 8-14 1x/d (G)		1000 F		1500 F (lethargy, failure to right)	Wier et al. 1987
71	Gn Pig (Hartley)	once (GW)			500 (slight weakness directly after dosing)	1000 (moderate to severe weakness and prostration directly after dosing)	Shepard 1994b

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Reproductive							
72	Rat (Fischer- 344)	once (GW)		500 M			Ghanayem et al. 1987a
73	Rat (Fischer- 344)	4 d (GW)		1000 M			Grant et al. 1985
74	Rat (Fischer- 344)	Gd 11-13 (GW)		300 F		600 F (vaginal bleeding)	NTP 1989
75	Rat (Fischer- 344)	Gd 9-11 (GW)		100 F		200 F (increased resorptions, implantation loss, vaginal bleeding)	NTP 1989
76	Rat (Fischer- 344)	Gd 11-13 (GW)		100 F		300 F (increased resorptions, implantation loss, vaginal bleeding)	NTP 1989
77	Rat (F344/N)	2 wk (W)		346 M			NTP 1993
78	Mouse (CD-1)	Gd 6-13 1x/d (GW)				1180 F (19% decrease in incidence of viable litters)	Hardin et al. 1987; Schuler et al. 1984

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to figure ^a	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
79	Mouse (CD-1)	Gd 8-14 (G)		650 F		1000 F (increased incidence of resorptions)	Wier et al. 1987
Developmental							
80	Rat (Fischer- 344)	Gd 9-11 (GW)		150 F	300 F (decreased fetal weight)		NTP 1989
81	Rat (Fischer- 344)	Gd 11-13 (GW)		300 F	600 F (decreased fetal body weight, decreased gravid uterine weight)		NTP 1989
82	Rat (Fischer- 344)	Gd 9-11 (GW)		200			NTP 1989
83	Rat (Fischer- 344)	Gd 11-13 (GW)		300			NTP 1989
84	Mouse (CD-1)	Gd 8-14 1x/d (G)		650		1000 (cleft palate in 1/5 litters)	Wier et al. 1987

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
INTERMEDIATE EXPOSURE							
Death							
85	Rat (CrI:COBS CD (SD)BR)	23 d 5 d/wk (G)				885 M (death in 1/9)	Eastman Kodak 1983; Krasavage 1986
86	Mouse (Swiss CD-1)	21 wk (W)				1300 F (death in 6/20)	Heindel et al. 1990
87	Mouse (JCL-ICR)	5 wk 5 d/wk (GO or GW)				2000 M (5/5 dead)	Nagano et al. 1979, 1984
Systemic							
88	Rat (Sherman)	90 d (F)	Resp	1540			Carpenter et al. 1956
			Hemato Hepatic	1540 76	310	(unspecified increase in relative liver weight)	
			Renal	310	1540	(unspecified increase in relative kidney weight)	
			Bd Wt	310	1540	(unspecified decrease in body weight gain)	

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
89	Rat (CrI:COBS CD (SD)BR)	6 wk 5 d/wk (G)	Resp	885 M			Eastman Kodak 1983; Krasavage 1986
			Cardio	885 M			
			Gastro		222M (mild hyperkeratosis and acanthosis in stomach)		
			Hemato			222 M (12% decreased RBC count, 7% decreased HGB, 6% increased MCH, hemoglobinuria)	
			Hepatic	222 M	443M (focal hemosiderin deposition, 30% increase in serum alkaline phosphatase activity)		
			Renal	222 M	443M (focal hemosiderin deposition in the proximal convoluted tubules)		
			Endocr	885 M			
			Ocular	885 M			
			Bd Wt	443 M	885M (7-12% decreased body weight gain in the presence of reduced feed consumption)		
Other	443 M	885M (12-31% reduced feed consumption during days 0-20)					

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
90	Rat (Sprague- Dawley)	21 d (W)	Hepatic	506 M 444 F			Exon et al. 1991
			Renal	506 M 444 F			
			Bd Wt	506 M 444 F			
			Other	180 M	506 M (12% decreased water consumption)		
				204 F	444 F (31% decreased water consumption)		

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
91	Rat (F344/N)	13 wk (W)	Resp	452 M 470 F			NTP 1993
			Cardio	452 M 470 F			
			Gastro	367 M 363 F	452 M (diarrhea) 470 F (diarrhea)		
			Hemato	129 M		281 M (decreased RBC, mild anemia) 82 F (decreased RBC, HCT, HGB)	
			Musc/skel	452 M 470 F			
			Hepatic		69 ^c M (hepatocellular 82 F alteration-cells that stained eosinophilic and lacked cytoplasmic granularity)		
			Renal		69 M (moderate increase in blood urea nitrogen) 82 F (decreased urine volume, possibly due to dehydration)		
			Endocr	452 M 470 F			
			Dermal	452 M 470 F			
			Ocular	452 M 470 F			
			Bd Wt	281 M 304 F	367 M (mean body weight gains decreased 12.5%)	452 M (24% decrease in body weight gain) 363 F (12% decreased final body weight and 32.5% decrease in body weight gain)	
			Other	69 M 82 F	129 M (water consumption decreased 12.1%) 151 F (water consumption decreased 17.6%)		

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
92	Rat (F344/N)	60 d (W)	Bd Wt	234 M	443 M (13% decrease in mean body weight gain)		NTP 1993
93	Rat (DW albino)	91-93 d (F)	Resp	919 M			Weil 1963
				976 F			
			Cardio	919 M			
				976 F			
			Gastro	919 M			
				976 F			
			Hepatic	188 M	919 M (25% increase in relative liver weight)		
				222 F	976 F (27% increase in relative liver weight)		
			Renal	188 M	919 M (18% increase in relative kidney weight)		
				222 F	976 F (23% increase in relative kidney weight)		
Endocr	919 M						
	976 F						
Bd Wt	28 M	188 M (body weight 91-7% less than controls over the course of the study)	919 M (body weight gain 53% lower than controls)				
	222 F		976 F (body weight gain 45% lower than controls)				
Other	28 M	188 M (food intake 18% lower than controls)					
	222 F	976 F (food intake 23% lower than controls)					

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
94	Mouse (Swiss CD-1)	25 wk (W)	Hepatic	1300			Heindel et al. 1990
			Renal		1300	(13-22% increase in kidney weight)	
			Bd Wt	1300 M	1300 F	(10% decrease in terminal body weight)	
			Other		700	(unspecified low water consumption)	
95	Mouse (Swiss CD-1)	14 wk (W)	Hepatic		700	(6-9% increase in absolute liver weight)	Heindel et al. 1990
			Renal	700 M	700 F	(22% increase in absolute kidney/adrenal weight)	
			Bd Wt	700			
96	Mouse (JCL-ICR)	5 wk 5 d/wk (G)	Hemato			500 M (decrease in RBC count)	Nagano et al. 1979, 1984

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference						
					Less Serious (mg/kg/day)	Serious (mg/kg/day)							
97	Mouse (B6C3F1)	13 wk (W)	Resp	694 M 1306 F	553 M (18.5% decreased body weight gain)	676 F (26.1% decreased mean body weight gain; 10% decreased mean final body weight)	NTP 1993						
			Cardio	694 M 1306 F									
			Gastro	694 M 1306 F									
			Musc/skel	694 M 1306 F									
			Hepatic	694 M 1306 F									
			Renal	694 M 1306 F									
			Endocr	694 M 1306 F									
			Dermal	694 M 1306 F									
			Ocular	694 M 1306 F									
			Bd Wt	223 M 370 F									
			Immunological/Lymphoreticular										
			98	Rat (CrI:COBS CD (SD)BR)				6 wk 5 d/wk (G)		222 M	443 M (enlarged, dark spleen in 3/9, 57% increase in spleen weight)		Eastman Kodak 1983; Krasavage 1986

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to figure ^a	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
99	Rat (Sprague- Dawley)	21 d (W)		506 M 444 F			Exon et al. 1991
100	Rat (F344/N)	13 wk (W)		69 M 82 F	129 M (increased hemosiderin 151 F pigmentation in spleen)		NTP 1993
101	Mouse (B6C3F1)	13 wk (W)		694 M 1306 F			NTP 1993
Neurological							
102	Rat (CrI:COBS CD (SD)BR)	6 wk 5 d/wk (G)		222 M			Eastman Kodak 1983; Krasavage 1986
103	Rat (F344/N)	13 wk (W)		452 M 470 F			NTP 1993
104	Mouse (B6C3F1)	13 wk (W)		694 M 1306 F			NTP1993
Reproductive							
105	Rat (CrI:COBS CD (SD)BR)	6 wk 5 d/wk (G)		885 M			Eastman Kodak 1983; Krasavage 1986

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
106	Rat (Sprague- Dawley)	21 d (W)		506 M			Exon et al. 1991
107	Rat (F344/N)	13 wk (W)		129 M	281 M (11.3% decreased sperm concentration)		NTP 1993
				304 F			
108	Rat (F344/N)	60 d (W)		443 M			NTP 1993
109	Mouse (Swiss CD-1)	21 wk (W)		700		1300 (21% decrease in litters/pair, 51% decrease in pups/litter)	Heindel et al. 1990
110	Mouse (Swiss CD-1)	25 wk (W)				1300 F (58% decrease in fertility, 66% decrease in live pups per litter; altered estrous cycle)	Heindel et al. 1990
111	Mouse (Swiss CD-1)	14 wk (W)		700			Heindel et al. 1990
112	Mouse (JCL-ICR)	5 wk 5 d/wk (G)		1000 M			Nagano et al. 1979, 1984

Table 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (continued)

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
113	Mouse (B6C3F1)	13 wk (W)		694 M 1306 F			NTP 1993
Developmental							
114	Mouse (Swiss CD-1)	21 wk (W)			700	(decrease in live pup weight)	Heindel et al. 1990
115	Mouse (Swiss CD-1)	14 wk (W)		700			Heindel et al. 1990

^aThe number corresponds to entries in Figure 2-3. Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

^bUsed to derive an acute oral minimal risk level (MRL) of 0.4 mg/kg/day; dose divided by an uncertainty factor of 90 (10 for use of a LOAEL, 3 for extrapolation from animals to humans, and 3 for human variability). For further details, see MRL worksheets in Appendix A.

^cUsed to derive an intermediate oral MRL of 0.07 mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability). For further details, see MRL worksheets in Appendix A.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Gn Pig = guinea pig; (GO) = gavage in oil; (GW) = gavage in water; HCT = hematocrit; Hemato = hematological; HGB = hemoglobin; (IN) = ingestion; LD₅₀ = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; PCV = packed cell volume; RBC = red blood cell; Resp = respiratory; (W) = water; WBC = white blood cell; wk = week(s); x = times.

Table 2-4. Levels of Significant Exposure to 2-Butoxyethanol Acetate - Oral

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Rat (Wistar)	once (GO)				3000 M (LD ₅₀) 2400 F (LD ₅₀)	Truhaut et al. 1979

^a The number corresponds to entries in Figure 2-4. Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 2-4. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

F = female; (GO) = gavage with oil; LD₅₀ = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level

Figure 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral
Acute (≤14 days)

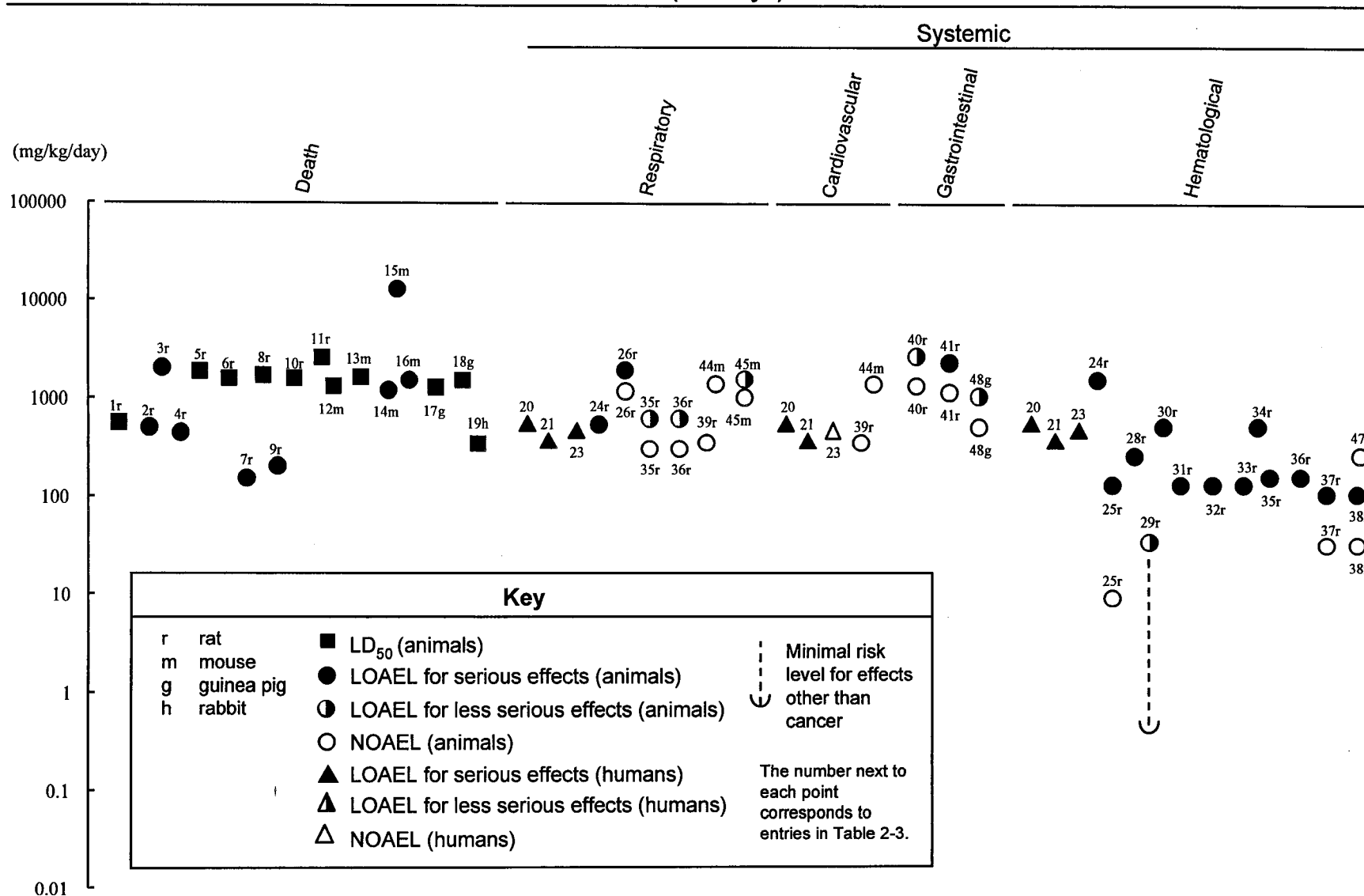


Figure 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (cont.)

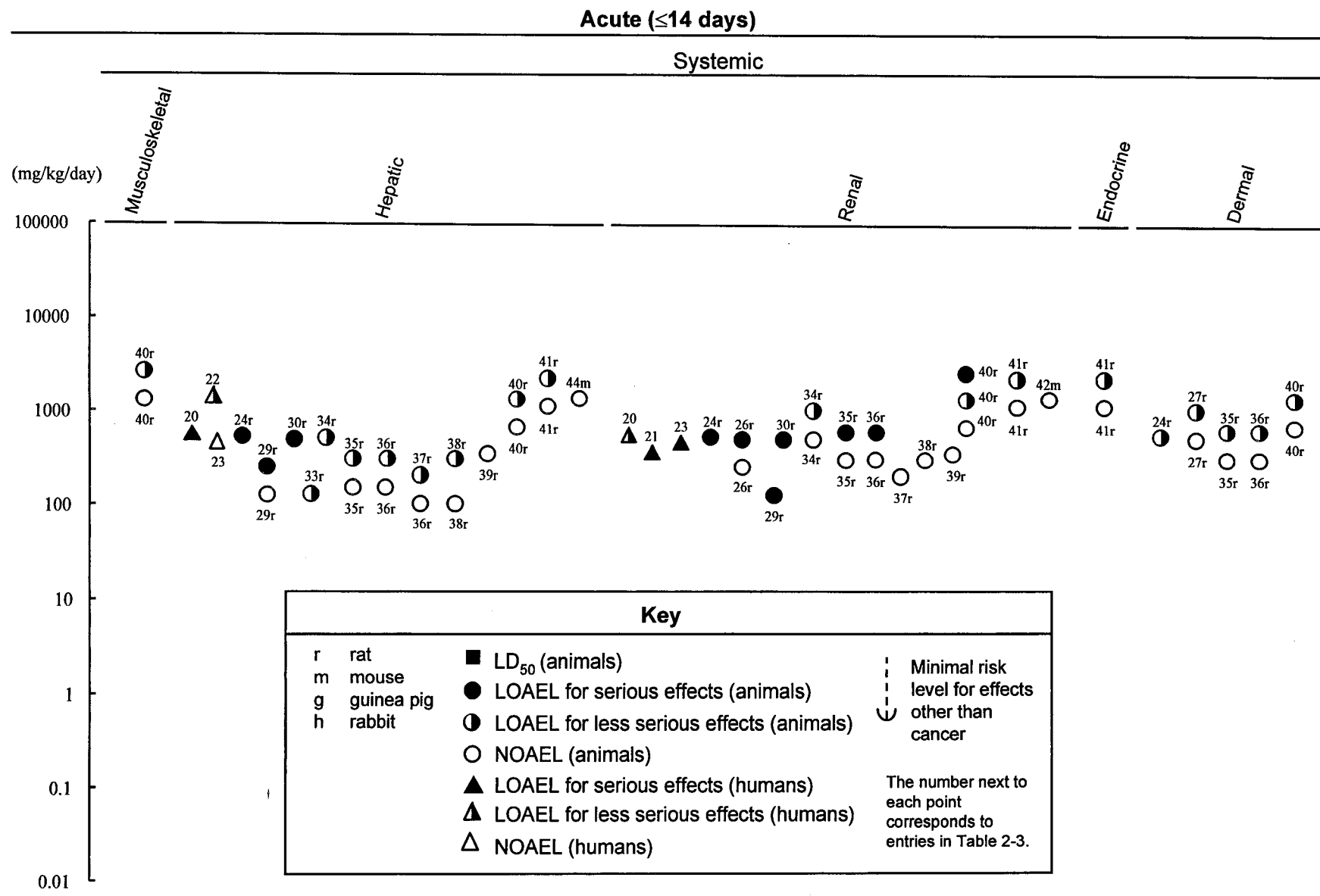


Figure 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (cont.)
Acute (≤ 14 days)

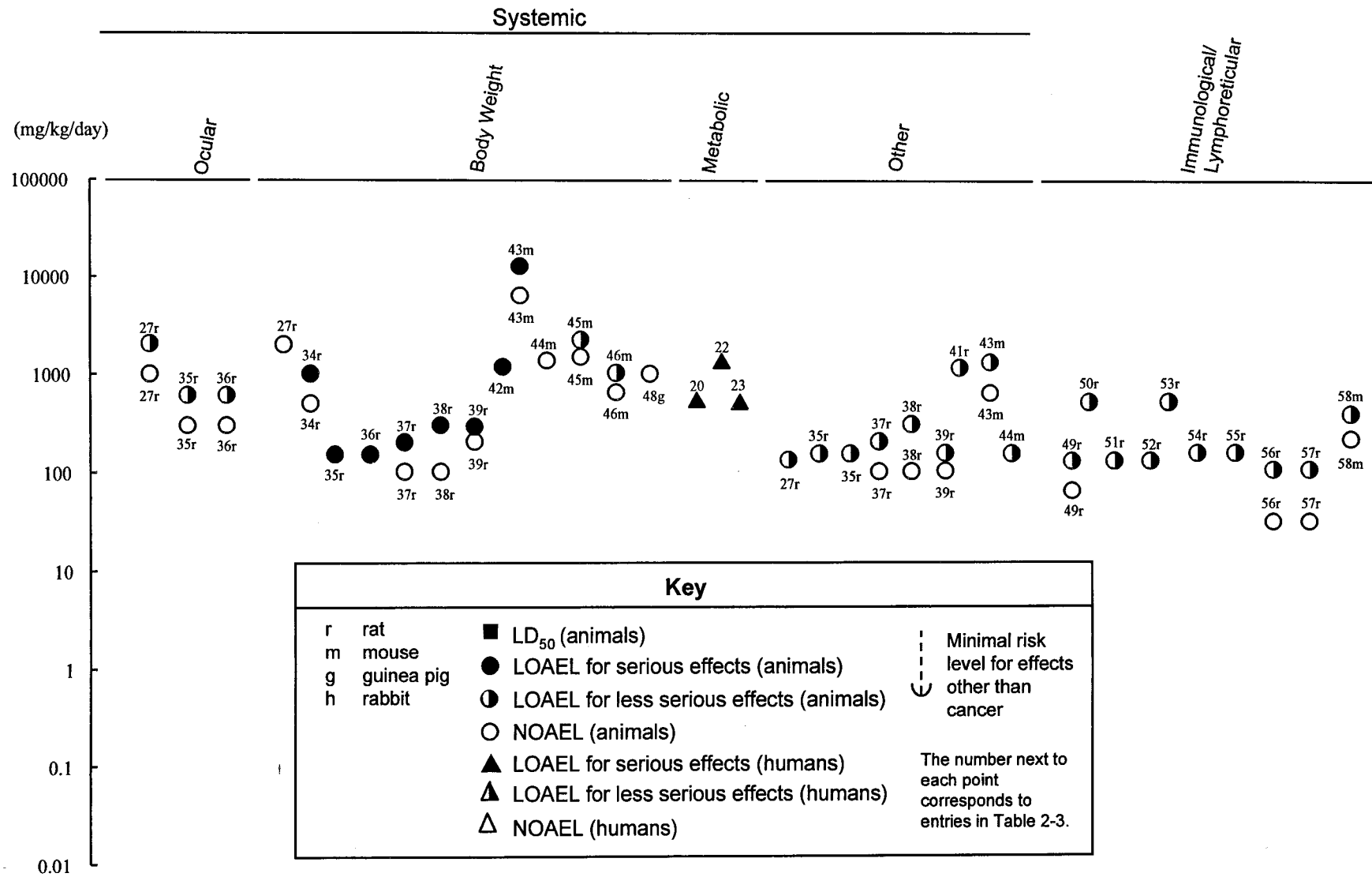


Figure 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (cont.)
Acute (≤ 14 days)

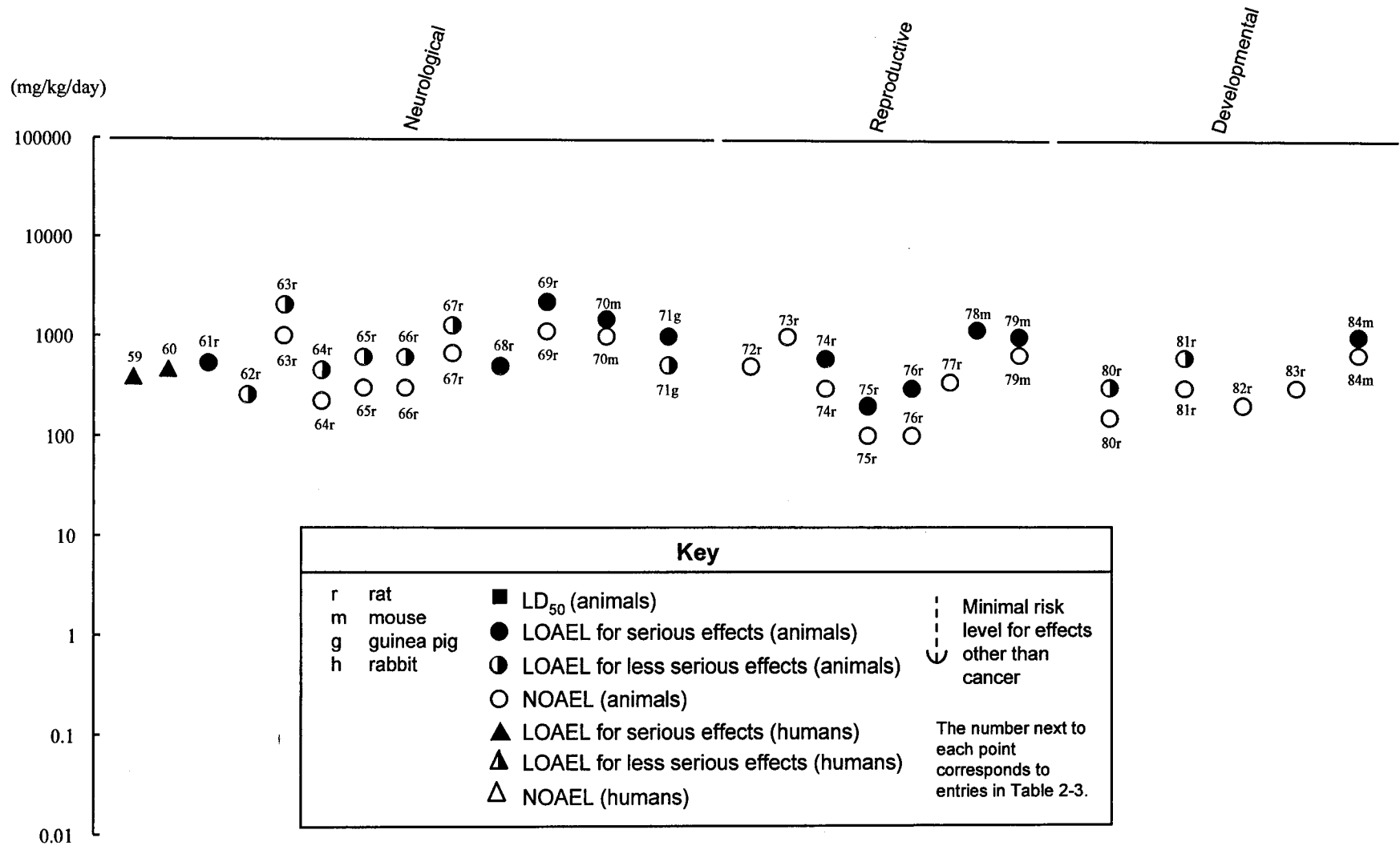


Figure 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (cont.)

Intermediate (15-364 days)

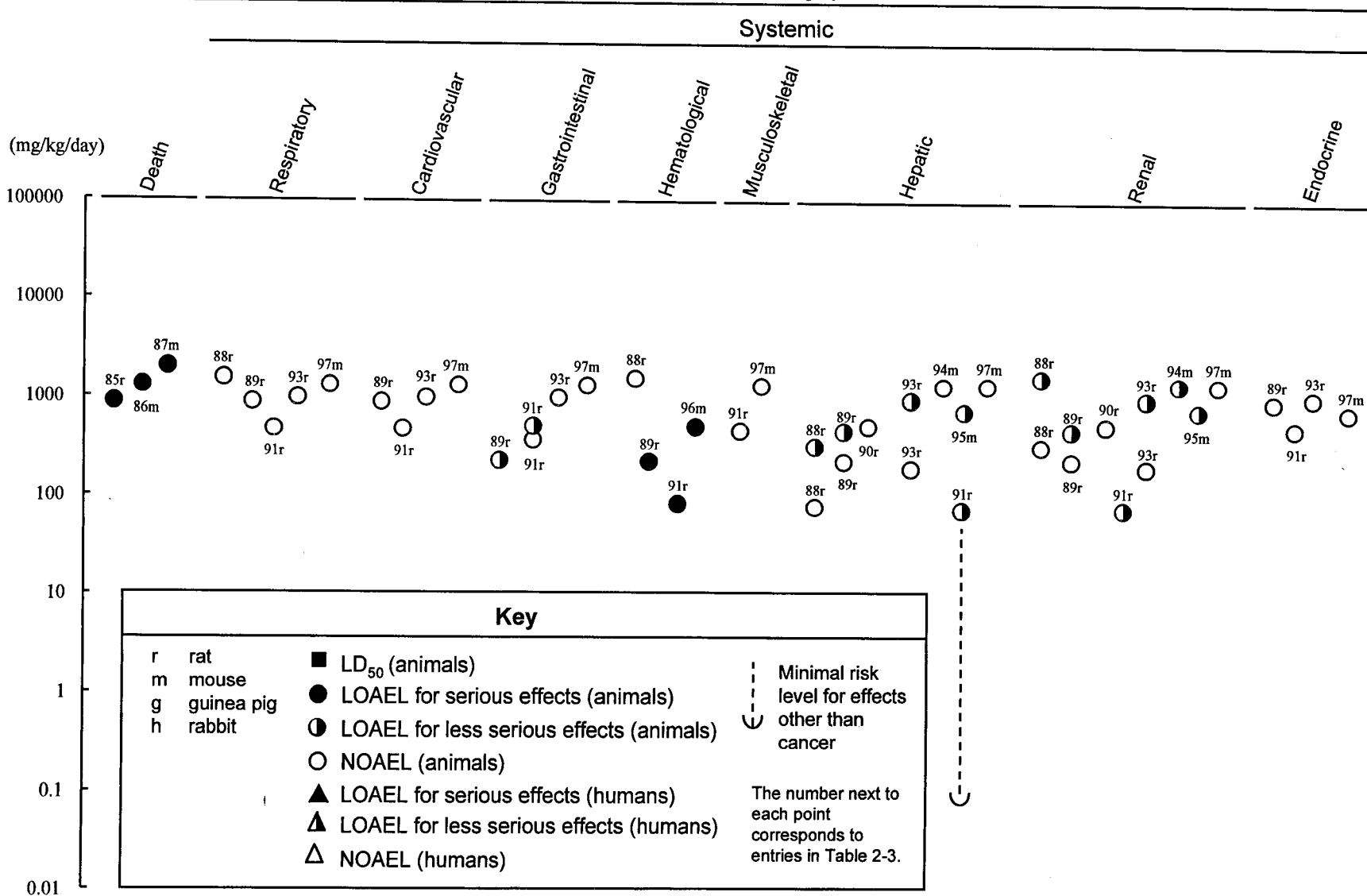


Figure 2-3. Levels of Significant Exposure to 2-Butoxyethanol - Oral (cont.)
Intermediate (15-364 days)

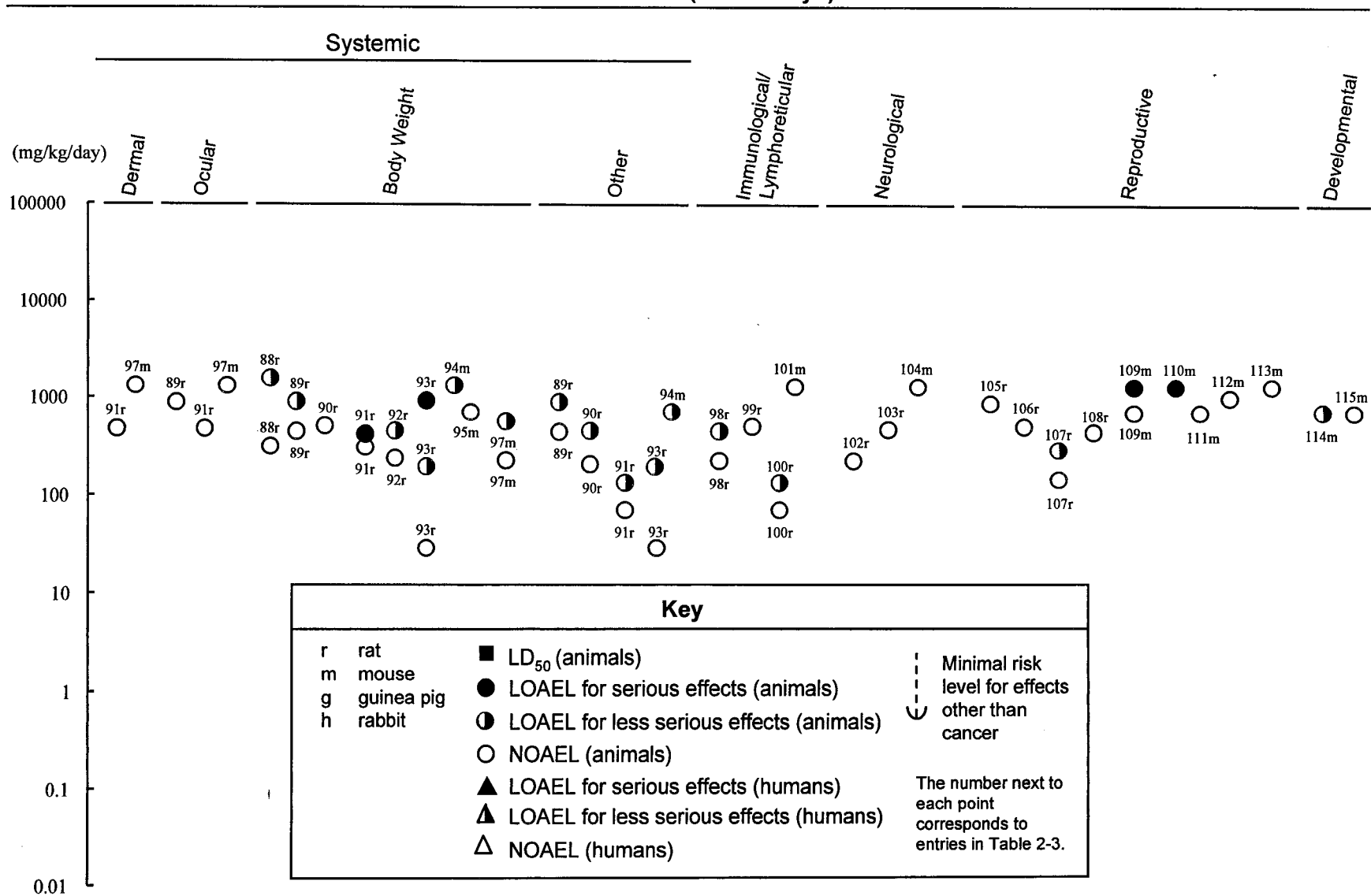


Figure 2-4. Levels of Significant Exposure to 2-Butoxyethanol Acetate - Oral
Acute (≤ 14 days)

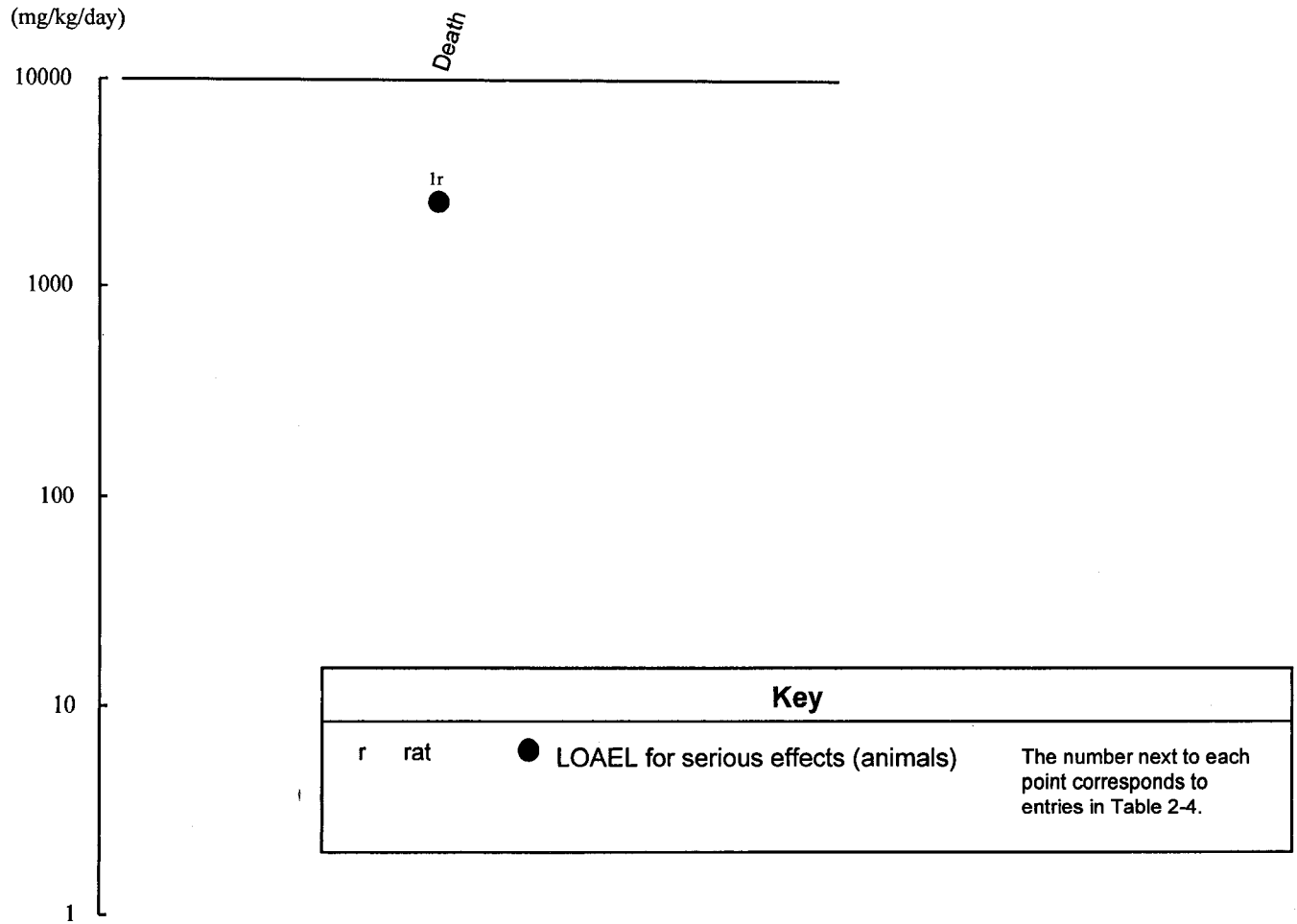


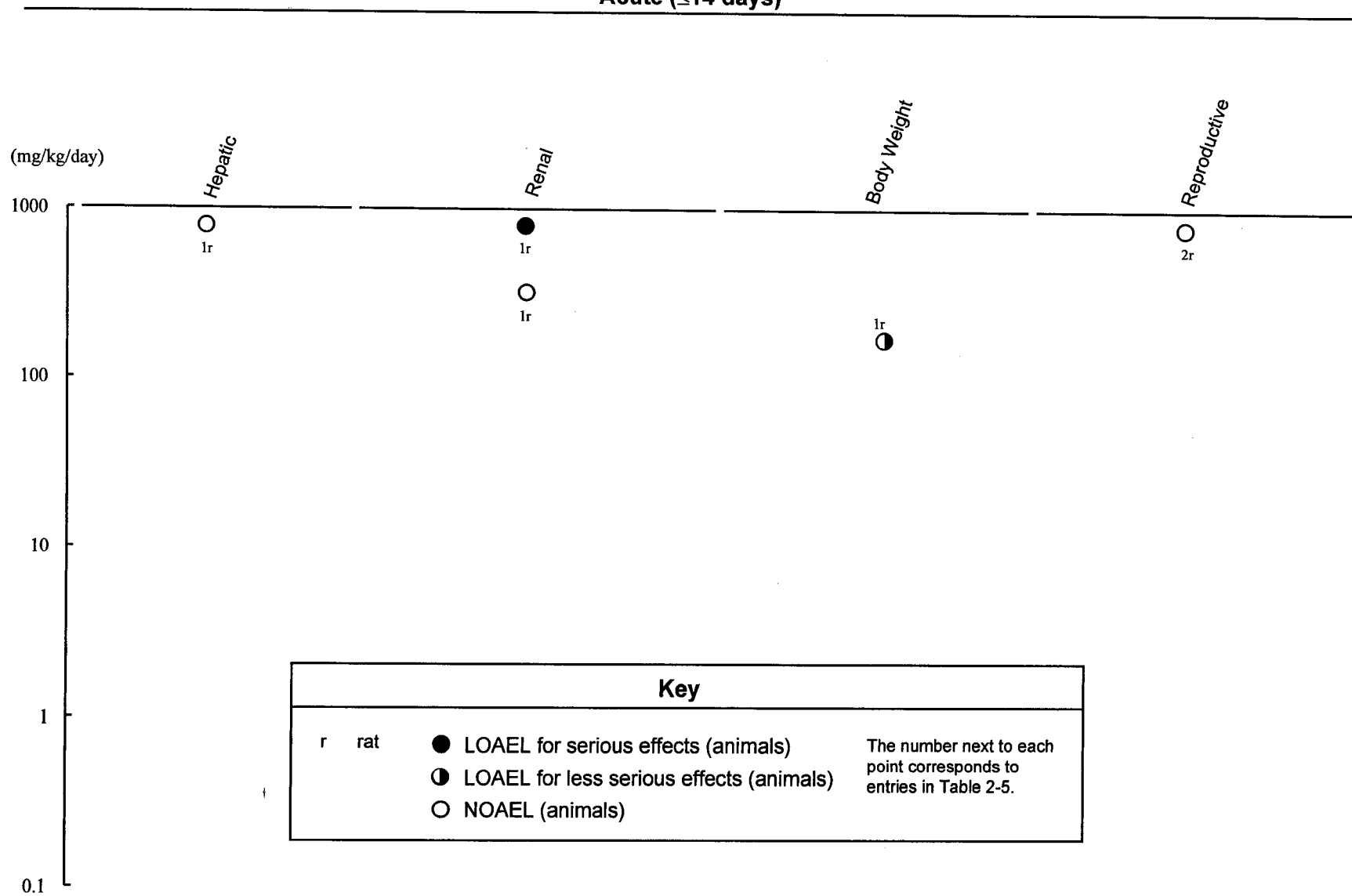
Table 2-5. Levels of Significant Exposure to Butoxyacetic Acid - Oral

Key to ^a figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Systemic							
1	Rat (Alpk/AP)	once (GW)	Hepatic	868 M			Foster et al. 1987
			Renal Bd Wt	434 M	174M (unspecified decrease in body weight gain)	868 M (hematuria)	
Reproductive							
2	Rat (Alpk/AP)	once (GW)		868 M			Foster et al. 1987

^a The number corresponds to entries in Figure 2-5.

Bd Wt = body weight; (GW) = gavage in water; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level

Figure 2-5. Levels of Significant Exposure to 2-Butoxyethanol Acid - Oral
Acute (≤ 14 days)



2. HEALTH EFFECTS

Animals also exhibit abnormal breathing after ingestion of high doses of 2-butoxyethanol. Female Fischer 344 rats had rapid, shallow, or difficult breathing after a single gavage dose of 2,000 mg/kg 2-butoxyethanol (Dow 1981) or a single gavage dose of 4,510 or 9,019 mg/kg (Union Carbide 1980b). The 2,000-mg/kg dose resulted in the death of two of three of the rats treated (Dow 1981), while all rats (five in each group) treated with 4,510 mg/kg or 9,019 mg/kg died (Union Carbide 1980b). Rats (Wistar, Sherman, and Carworth-Wistar) also exhibited congested or hemorrhaged lungs at death after a gavage dose of 530 mg/kg (Carpenter et al. 1956). However, no overt respiratory effects were seen in Fischer 344 rats or B6C3F₁ mice after ingestion of 2-butoxyethanol at doses of ≤ 346 mg/kg/day (males) or ≤ 265 mg/kg/day (females) for rats and ≤ 627 mg/kg/day (males) or $\leq 1,364$ mg/kg/day (females) for mice in drinking water for 2 weeks (NTP 1993). Pregnant Fischer 344 rats exhibited dyspnea after oral dosing by gavage in a preliminary teratology study with 600 mg/kg/day 2-butoxyethanol on gestational days 9-11 or 11-13 (NTP 1989). In the definitive study, no respiratory effects were noted at doses ≤ 200 mg/kg/day on gestational days 9-11 or ≤ 300 mg/kg/day on gestational days 11-13 (NTP 1989). However, in mated CD-1 mice given 0, 350, 650, 1,000, 1,500, or 2,000 mg/kg/day 2-butoxyethanol by gavage on gestational days 8-14, abnormal breathing was observed at doses of 1,500 and 2,000 mg/kg/day (Wier et al. 1987). These doses resulted in the deaths of three of six mice at 1,500 mg/kg/day and six of six mice at 2,000 mg/kg.

In intermediate-duration studies, no overt signs of respiratory effects were found in male and female Sherman rats after ingestion of $\leq 1,540$ mg/kg/day 2-butoxyethanol in the feed for 90 days (Carpenter et al. 1956). No overt signs of respiratory effects and no gross or histologically observed lung or nasal cavity lesions were observed in male COBS CD (SD)BR rats receiving 885 mg/kg/day by gavage for 6 weeks (Eastman Kodak 1983; Krasavage 1986) or in Fischer 344 rats receiving doses ≤ 452 mg/kg/day (males) and ≤ 470 mg/kg/day (females) or B6C3F₁ mice receiving ≤ 694 mg/kg/day (males) and $\leq 1,306$ mg/kg/day (females) in drinking water for 13 weeks (NTP 1993). In addition, no histopathological lesions were found in the nasal turbinates of rats or mice in the NTP (1993) 13-week drinking water study. Histopathological changes in the lungs were not observed in DW Albino rats treated with 2-butoxyethanol at doses up to 919 mg/kg/day for males and 976 mg/kg/day for females (Weil and Carpenter 1963).

Rats given unspecified acute oral doses of 2-butoxyethanol acetate in olive oil as part of a lethality study exhibited no adverse respiratory clinical signs or gross or histopathological changes in the lungs (Truhaut et al. 1979).

2. HEALTH EFFECTS

Cardiovascular Effects. An 87-year-old woman died from cardiac arrest 3 days after she ingested an unknown amount of a cleaner containing 6.5% 2-butoxyethanol (Litovitz et al. 1991). Before death she also experienced hypotension and ventricular tachycardia and arrhythmias. Ingestion of 2-butoxyethanol has been associated with cardiovascular effects including tachycardia, and low blood pressure in a patient who ingested 650 mg/kg (Bauer et al. 1992) and low blood pressure in a patient who ingested 391 mg/kg (Gijzenbergh et al. 1989). However, in another case report of a woman who ingested 467-933 mg/kg, no noticeable cardiovascular effects were observed (Rambourg-Schepens et al. 1988). In addition, two children who accidentally ingested 290 or 1,862 mg/kg 2-butoxyethanol did not exhibit adverse cardiovascular effects (Dean and Krenzelok 1992). Gastric emptying by administration of syrup of ipecac or by gastric lavage within minutes or hours of ingestion (time not specified) may have prevented any adverse effects.

2-Butoxyethanol does not appear to cause cardiovascular effects in animals after oral exposure. In Fischer 344 rats receiving ≤ 346 mg/kg/day (males) and ≤ 265 mg/kg/day (females) and in B6C3F₁ mice receiving ≤ 627 mg/kg/day (males) and $\leq 1,364$ mg/kg/day (females) in the drinking water for 2 weeks, no changes in the heart weight and no gross pathological lesions were observed in hearts (NTP 1993). Similarly, in Fischer 344 rats receiving ≤ 452 mg/kg/day (males) and ≤ 470 mg/kg/day (females) and in B6C3F₁ mice receiving ≤ 694 mg/kg/day (males) and $\leq 1,306$ mg/kg/day (females) in the drinking water for 13 weeks, no changes in heart weight and no gross or histologically observed lesions were observed in the heart or the aorta (NTP 1993). No effects on heart weight and no histopathological lesions in the heart were observed in adult male COBS CD (SD)BR rats given undiluted 2-butoxyethanol by gavage at doses of 0, 222, 443, or 885 mg/kg/day, 5 days per week, over a 6-week period (Eastman Kodak 1983; Krasavage 1986). Cardiovascular effects were not observed in DW Albino rats provided with 2-butoxyethanol in the drinking water for 91-93 days at doses of 919 mg/kg/day for males and 976 mg/kg/day for females (Weil and Carpenter 1963).

Male and female rats given acute oral doses of 2-butoxyethanol acetate in olive oil as part of a lethality study exhibited no adverse cardiovascular clinical signs or gross or histopathological lesions in the heart (Truhaut et al. 1979).

Gastrointestinal Effects. Very little information is available to describe gastrointestinal effects of 2-butoxyethanol by oral exposure. Wistar rats exhibited distended stomachs filled with liquid and gas, and bloody intestines at necropsy after single gavage doses of 2,255-9,019 mg/kg 2-butoxyethanol (Union Carbide 1980b). At 2,244 mg/kg, two of five rats died, while five of five rats died at each of the two highest

2. HEALTH EFFECTS

doses (4,510 and 9,019 mg/kg). Very red small intestines were noted 1 of 10 male Wistar rats after a single gavage dose of 2,560 mg/kg 2-butoxyethanol, a dose that resulted in the death of 9 of 10 treated animals (Olin 1976). Moderate-to-mild necrosis and hemorrhage of the gastric mucosa were observed in one of five male guinea pigs and one of five female guinea pigs treated with a single gavage dose of 1,000 mg/kg 2-butoxyethanol in water, a dose that resulted in the death of one of each sex; the contribution of the gavage procedure to these gastric effects is unclear, since there were no controls in this experiment (Shepard 1994b). Male COBS CD (SD)BR rats showed mild hyperkeratosis and acanthosis of the stomach after gavage doses of 222-885 mg/kg/day 2-butoxyethanol, 5 days per week, for 6 weeks (Eastman Kodak 1983; Krasavage 1986). No gross pathological or histopathological lesions were found in the esophagus, cecum, colon, duodenum, jejunum, or ileum. No gross or histopathological changes were observed in the esophagus, stomach, duodenum, or colon of DW Albino rats treated with 2-butoxyethanol in the diet for 3 months at doses up to 919 mg/kg/day for males and 976 mg/kg/day for females (Weil and Carpenter 1963). Diarrhea was noted in Fischer 344 rats receiving 452 mg/kg/day (males) and 470 mg/kg/day (females) 2-butoxyethanol in the drinking water for 13 weeks, although this effect was not observed at lower doses (≤ 367 mg/kg/day) (NTP 1993). In the same study, B6C3F₁ mice ingesting ≤ 694 mg/kg/day (males) and $\leq 1,306$ mg/kg/day (females) 2-butoxyethanol in the drinking water for 13 weeks did not develop diarrhea. In addition, gross and histological examination of the esophagus, cecum, colon, rectum, duodenum, jejunum, ileum, and stomach of the rats and the mice in the 13-week drinking water study revealed no lesions.

Hematological Effects. A male patient who was an abuser of alcohol and had a history of trichloroethylene ingestion was admitted to the hospital after ingesting 650 mg/kg 2-butoxyethanol. He exhibited nonhemolytic anemia, low prothrombin time (longer time to clotting), and thrombopenia (Bauer et al. 1992). Progressive erythropenia and hemoglobinuria were noted after a woman ingested 467-933 mg/kg 2-butoxyethanol (Rambourg-Schepens et al. 1988), and a decrease in blood hemoglobin was noted in a woman who ingested 391-469 mg/kg 2-butoxyethanol (Gijzenbergh et al. 1989). Hemodialysis, used in two of these cases (Bauer et al. 1992; Gijzenbergh et al. 1989), may have contributed to hematological effects. Intravascular coagulation was observed in an 87-year-old women who died of cardiac arrest 3 days after ingesting an unknown amount of cleaner containing 6.5% 2-butoxyethanol (Litovitz et al. 1991). Two children who accidentally ingested 290 or 1,862 mg/kg 2-butoxyethanol exhibited no adverse hematological effects (Dean and Krenzelok 1992). Gastric emptying by administration of syrup of ipecac or by gastric lavage within minutes or hours of ingestion (time not specified) may have prevented any adverse effects. Hematologic effects were also not observed in a man who ingested two doses of a concentrated glass cleaner 12 days apart (Gualtieri et al. 1995). On the first occasion he ingested 1,006-1,341 mg/kg; on the second

2. HEALTH EFFECTS

occasion he ingested 1,341 mg/kg. After both doses, this case report indicates that the man was treated with hemodialysis and ethanol. The treatment occurred within 8 hours of the second ingestion, but it is unclear from this report how much time elapsed between the first ingestion and treatment and whether there might have been hematological consequences had these treatments not taken place.

Hemolysis and hemoglobinuria are common observations in animals treated orally with 2-butoxyethanol for acute durations (Carpenter et al. 1956; Corley et al. 1994; Dow 1959; Ghanayem and Sullivan 1993; Ghanayem et al. 1987a, 1987b, 1990b, 1992; Grant et al. 1985; NTP 1989). After Wistar, Sherman, and Cat-worth-Wistar rats were given single doses of 2-butoxyethanol by gavage, hemoglobinuria was observed in male rats at 3,000 mg/kg and in female rats at 1,500 mg/kg (Carpenter et al. 1956). These doses are in the range of the LD₅₀ given by Carpenter et al. (1956). Male Fischer 344 rats receiving a single dose of 500 mg/kg 2-butoxyethanol by gavage exhibited hemolysis of erythrocytes accompanied by a drastic increase in the concentration of free hemoglobin in the plasma (Ghanayem et al. 1987b); hemoglobinuria was observed in all rats. In the same experiment, rats receiving a single dose of 125 mg/kg 2-butoxyethanol exhibited the same effects, although to a lesser degree. Hematology profiles of male Fischer 344 rats treated with single doses of 125-500 mg/kg 2-butoxyethanol by gavage indicated changes at ≥ 125 mg/kg that are characteristic of hemolysis, including increased hematocrit, packed cell volumes, and mean cell volume, followed by a decrease in these parameters as hemolysis progressed (Ghanayem et al. 1990b). In male Fischer 344 rats given 250 mg/kg 2-butoxyethanol by gavage, hemolysis was noted, characterized by an increase in mean cell volume and hematocrit, followed by a decline in hemoglobin concentration and red blood cell count (Ghanayem and Sullivan 1993). Mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration initially increased and then declined. In the same study, guinea pigs dosed once with 250 mg/kg 2-butoxyethanol had no adverse hematological effects. In a metabolism study, in which male Fischer 344 rats received radiolabeled 2-butoxyethanol at doses of 8.6 and 126 mg/kg by gavage in water, two rats in the high-dose group exhibited hemolysis and hemoglobinuria (Corley et al. 1994). These effects were not observed in rats that received 8.6 mg/kg.

In another study in male Fischer 344 rats that received 125 mg/kg/day 2-butoxyethanol by gavage for 1, 2, 3, 6, or 12 consecutive days, hemolytic anemia was noted after treatment for 1-3 days, but subsided with longer exposure (Ghanayem et al. 1992). In the same study, 125 mg/kg 2-butoxyethanol was administered to rats for 3 days; the animals were then allowed to recover for 7 days. Additional treatment with 125 or 250 mg/kg 2-butoxyethanol caused a decrease in red blood cell count and hemoglobin. In male rats that were first bled and then allowed a 7-day recovery period, increased hematocrit and reticulocytes were observed in these rats

2. HEALTH EFFECTS

after treatment with 125 mg/kg 2-butoxyethanol. The purpose of the bleeding/recovery experiment was to assess the effect of 2-butoxyethanol on a hematopoietic system that was already responding to a depletion of red blood cells (Ghanayem et al. 1992). That pretreatment with 2-butoxyethanol is protective has also been shown by Sivarao and Mehendale (1995). In this study, blood taken from rats 7 days after treatment with a single gavage dose of 500 mg/kg 2-butoxyethanol in water was less sensitive to the hemolytic effects of the 2-butoxyethanol metabolite, 2-butoxyacetic acid, than blood taken 21 days after treatment.

Male Fischer 344 rats treated by gavage with 500 mg/kg/day 2-butoxyethanol for 4 days showed reduced red blood cell count and hemoglobin and increased mean corpuscular volume, reticulocyte counts, and mean corpuscular hemoglobin, with bone marrow hyperplasia (Grant et al. 1985). Pregnant Fischer 344 rats exhibited increased reticulocyte counts, mean corpuscular volume, mean corpuscular hemoglobin, and platelet count, and decreased red blood cell count, hemoglobin, hematocrit, and mean corpuscular hemoglobin concentration after oral dosing in a preliminary teratology study with 150 mg/kg/day 2-butoxyethanol on gestational days 9-11 or 11-13, or on gestational day 20 (NTP 1989). In the definitive study, similar effects were noted at 100 mg/kg/day on gestational days 9-11 or gestational days 11-13 (NTP 1989).

In a study showing the age-dependent hemolytic effects of 2-butoxyethanol, young (4-5 weeks) and adult (9-13 weeks, 5-6 months, and 16 months) F344 rats were dosed with 0, 32, 63, 125, 250, or 500 mg/kg 2-butoxyethanol in water by gavage (Ghanayem et al. 1987a). Hematotoxicity of 2-butoxyethanol was monitored for 48 hours. In younger rats, 125 mg/kg caused no effect on hematological parameters. At 500 mg/kg, red blood cell count, hemoglobin, and hematocrit were decreased, although not as much as in the older rats. In older (9-13 weeks) rats, 2-butoxyethanol at 125 mg/kg caused severe acute hemolytic anemia resulting in significant decreases at 8 and 24 hours after treatment in red blood cell count, hemoglobin, and hematocrit, and increases 8 hours after administration in the concentration of free plasma hemoglobin. At 4 hours, peak increases in free plasma hemoglobin were seen in both younger (4-5 weeks) and older (9-13 weeks) rats dosed with 500 mg/kg. Older rats (9-13 weeks) were more susceptible to the hematotoxic effects of 2-butoxyethanol. Secondary to the hemolytic effects, 2-butoxyethanol also caused hemoglobinuria. The onset of the development of hemoglobinuria paralleled the observed decline in the concentration of free hemoglobin in the plasma. In the 32-, 63-, and 125-mg/kg dose groups, 100% of the 16-month-old rats developed hemoglobinuria; hemoglobinuria was not monitored in 16-month-old rats receiving 250 or 500 mg/kg. At 6 months of age, 63 and 125 mg/kg caused hemoglobinuria; the same effect was not seen in younger rats (4-13 weeks) until doses reached 125 mg/kg. Further, both the hemolytic effects and the secondary effects of 2-butoxyethanol were age-dependent, with older (5-16 months) rats being more sensitive

2. HEALTH EFFECTS

than younger (4-13 weeks) rats. Young rats (4-5 weeks old) and adult rats (9-13 weeks old) were treated with 500 mg/kg 2-butoxyethanol and reticulocytes and leukocytes were counted up to 48 hours after treatment. Adult (9-13 weeks old) rats exhibited neutrophilic leukocytosis and mild lymphopenia within 4 hours. This was not detected at 48 hours. An absolute increase in reticulocyte count occurred at 48 hours after dosing. In young (4-5 weeks old) rats, an absolute increase in total leukocyte, band neutrophils, lymphocytes, and monocytes was observed at 48 hours, but there was no significant effect on reticulocyte count. Based on the LOAEL of 32 mg/kg for hematological effects in the aged rats in the study by Ghanayem et al. (1987a), an acute oral MRL of 0.4 mg/kg./day was calculated as described in the footnote to Table 2-3 and in Appendix A.

Hematological effects reflecting hemolysis have also been found in animals after intermediate-duration oral exposure to 2-butoxyethanol. In adult male COBS CD (SD)BR rats given undiluted 2-butoxyethanol by gavage at doses of 0, 222, 443, or 885 mg/kg/day, 5 days per week, over a 6-week period, dose-related decrease in red blood cell counts and hemoglobin and dose-related increase in mean corpuscular hemoglobin and hemoglobinuria were observed at all doses (Eastman Kodak 1983; Krasavage 1986). In a similar study, male JCL-ICR mice exhibited a decrease in red blood cell count after oral doses of 500 and 1,000 mg/kg/day of 2-butoxyethanol 5 days per week for 5 weeks (Nagano et al. 1979,1984). However, while no evidence of blood or hemoglobin pigments were found in the urine of male and female Sherman rats after ingestion of $\leq 1,540$ mg/kg/day 2-butoxyethanol in the feed for 90 days (Carpenter et al. 1956), methods were poorly discussed, and data were not shown. Decreased red blood cell count and mild anemia were noted in male Fischer 344 rats receiving ≥ 281 mg/kg/day 2-butoxyethanol, but not ≤ 129 mg/kg/day, and red blood cell count, hematocrit, and hemoglobin were decreased in female rats receiving ≤ 82 mg/kg/day (lowest dose in females) in the drinking water for 13 weeks (NTP 1993). No hematological effects were observed in male rats receiving 69 mg/kg/day (lowest dose in males). Hematological evaluations were not performed in the B6C3F₁ mice ingesting ≤ 694 mg/kg/day (males) and $\leq 1,306$ mg/kg/day (females) 2-butoxyethanol in the drinking water for 13 weeks (NTP 1993).

Male and female Wistar rats given unspecified acute oral doses of 2-butoxyethanol acetate in olive oil as part of a lethality study exhibited severe hemoglobinuria (Truhaut et al. 1979).

The hemolytic effects of 2-butoxyethanol and 2-butoxyethanol acetate in animals have been associated with changes in the spleen, including increased weight, engorgement, and increased hematopoiesis. These effects are discussed further in Section 2.2.2.3, Immunological and Lymphoreticular Effects.

2. HEALTH EFFECTS

Musculoskeletal Effects. Male Wistar rats given single oral doses of 2,560, or 5,000 mg/kg exhibited muscle flaccidity at 2,560 and 5,000 mg/kg (Glin 1976), doses which resulted in the death of 9 of 10 and 10 of 10 rats, respectively. Histological examination of thigh muscles and bones revealed no pathological lesions in Fischer 344 rats receiving doses of ≤ 452 mg/kg/day (males) and ≤ 470 mg/kg/day (females) and in B6C3F₁ mice receiving doses of ≤ 694 mg/kg/day (males) and $< 1,306$ mg/kg/day (females) 2-butoxyethanol in drinking water for 13 weeks (NTP 1993).

Hepatic Effects. No adverse hepatic effects were noted in a woman who ingested 467-933 mg/kg 2-butoxyethanol (Rambourg-Schepens et al. 1988). However, abnormal liver function (increase in aspartate aminotransferase) was noted in a man who had ingested 650 mg/kg 2-butoxyethanol (Bauer et al. 1992). The man was known to abuse alcohol and trichloroethylene, which probably contributed strongly to the abnormal liver function. In a man who ingested two doses of a concentrated glass cleaner containing 2-butoxyethanol 12 days apart, increased serum alanine aminotransferase, aspartate aminotransferase, and bilirubin were observed following the first ingestion (1,006-1,341 mg/kg) but not following the second ingestion (1,341 mg/kg) (Gualtieri et al. 1995). After both doses, this case report indicates that the man was treated with hemodialysis and ethanol; the treatment occurred within 8 hours of the second ingestion, but it is unclear how much time elapsed between the first ingestion and treatment and whether there might have been further hepatic effects had this treatment not taken place. Hepatic failure was reported in an 87-year-old woman who died of cardiac arrest 3 days after ingesting an unknown volume of glass cleaner containing 6.5% 2-butoxyethanol (Litovitz et al. 1991).

Hepatic effects have been observed in animals exposed orally to 2-butoxyethanol. Mottled livers were observed in Wistar, Sherman, and Car-worth-Wistar rats that died after receiving ≥ 530 mg/kg by gavage (Carpenter et al. 1956). Young (4-5 weeks) and adult (9-13 weeks) Fischer 344 rats were dosed with 0, 32, 63, 125, 250, or 500 mg/kg 2-butoxyethanol by gavage and then killed at 24 and 48 hours after dosing. The livers were weighed, fixed, and examined for histopathological lesions (Ghanayem et al. 1987a). Histopathological results were presented for the control, 125-, 250-, and 500-mg/kg dose groups. Secondary to the hemolytic effects, 2-butoxyethanol also caused histopathologic changes in the liver, consisting of focal coagulative necrosis of hepatocytes in one of six adult rats at 250 mg/kg and in five of six adult rats at 500 mg/kg; no effects were seen in young rats even at 500 mg/kg. This effect of 2-butoxyethanol was age-, dose- and time-dependent, with older rats being more sensitive. The hepatic effects were more severe at 24 hours after treatment and showed some recovery by 48 hours after treatment. Phagocytized hemoglobin was found in the hepatic parenchymal cells and Kupffer cells, which is consistent with the role of these cells

2. HEALTH EFFECTS

in hemoglobin degradation. However, although phagocytized hemoglobin was frequently present in or next to areas of focal necrosis, the role of phagocytized hemoglobin, if any, in the mechanism of this necrosis is not known. Male Fischer 344 rats receiving 500 mg/kg 2-butoxyethanol by gavage exhibited similar effects on hepatic tissue (Ghanayem et al. 1987b). Dark livers were observed at the necropsy of male Wistar rats that had been given one dose of 1,310 mg/kg (Olin 1976) or 2,255 mg/kg (Union Carbide 1980b) 2-butoxyethanol by gavage. In male Fischer 344 rats that received 125 mg/kg/day 2-butoxyethanol by gavage for 1, 2, 3, 6, or 12 consecutive days, a slight decrease in relative liver weight was noted after dosing for 3 or 6 days, followed by a slight increase after dosing for 12 days (Ghanayem et al. 1992). An increase in liver weight was also noted in male Fischer 344 rats after a gavage dose of 500 mg/kg/day 2-butoxyethanol for 4 days (Grant et al. 1985). However, no effects on liver weight and no gross pathological hepatic effects were seen in Fischer 344 rats receiving ≤ 346 mg/kg/day (males) and ≤ 265 mg/kg/day (females) or in B6C3F₁ mice receiving ≤ 627 mg/kg/day (males) and $\leq 1,364$ mg/kg/day (females) of 2-butoxyethanol in drinking water for 2 weeks (NTP 1993).

Pregnant Fischer 344 rats exhibited decreased absolute liver weight 24 hours after oral dosing in a preliminary teratology study at 300 and 600 mg/kg/day 2-butoxyethanol on gestational days 9-11 or 11-13 (NTP 1989). In the definitive study, decreased absolute maternal liver weight was noted at termination on gestational days 12 or 20 after dosing with 200 mg/kg/day on gestational days 9-11 and at termination on gestational day 14 after dosing with 300 mg/kg/day on gestational days 11-13 (NTP 1989).

Hepatic effects have also been observed in animals after intermediate oral exposure to 2-butoxyethanol. An unspecified increase in relative liver weight was reported for Sherman rats that received 1,540 mg/kg/day in the diet for 90 days (Carpenter et al. 1956). Absolute, but not relative, liver weight was only slightly increased (5%) in male Sprague-Dawley rats that received 180 mg/kg/day in the drinking water for 21 days (Exon et al. 1991). No increase in liver weight was observed in the female rats at ≤ 444 mg/kg/day or in the males at 506 mg/kg/day. Furthermore, histological examination of livers revealed no pathological lesions. In DW Albino rats treated with 2-butoxyethanol in the diet for 91-93 days, relative liver weights were increased by 25% in males at 919 mg/kg/day and 27% in females at 976 mg/kg/day (Weil and Carpenter 1963). This effect may have been associated with decreased body weight gain and food consumption. No effects on liver weight were noted at lower doses (188 mg/kg/day males, 222 mg/kg/day females), nor were any histopathological changes observed at any dose.

2. HEALTH EFFECTS

Adult male COBS CD (SD)BR rats given ≤ 885 mg/kg/day 2-butoxyethanol for 6 weeks showed increased relative, but not absolute, liver weight in all dose groups (≥ 222 mg/kg/day) (Eastman Kodak 1983; Krasavage 1986). Histological examination of livers revealed hemosiderin deposition in the liver at ≥ 443 mg/kg/day and hepatocytomegaly at 885 mg/kg/day. Statistically significant increases were found for serum alkaline phosphatase at ≥ 443 mg/kg/day and for serum alanine aminotransferase at 885 mg/kg/day.

In Fischer 344 rats exposed to 2-butoxyethanol in the drinking water for 13 weeks, no treatment-related changes in liver weight were observed (NTP 1993). Clinical chemistry evaluation revealed significantly increased levels of serum alkaline phosphatase in males (452 mg/kg/day) at 3 weeks and in females (363 and 470 mg/kg/day) at 13 weeks, and significantly increased levels of serum alanine aminotransferase in males (452 mg/kg/day) and in females (363 and 470 mg/kg/day) at 13 weeks. The increase in alkaline phosphatase levels is consistent with mild cholestasis, while increased serum alanine aminotransferase levels are consistent with hepatocellular necrosis. Histological examination of the livers revealed hepatocellular alterations (hepatocytes that stained more eosinophilic and lacked the amphophilic to basophilic granularity of the cytoplasm) at all doses (≥ 69 mg/kg/day for males and ≥ 82 mg/kg/day in females); centrilobular hepatocellular degeneration in males at ≥ 281 mg/kg/day and in females at ≥ 304 mg/kg/day; and brown to green granular pigment staining strongly positive for iron in Kupffer cell cytoplasm in males at 452 mg/kg/day and in females at ≥ 151 mg/kg/day. These lesions, particularly in the females, displayed both increased dose-related incidence and increased dose-related severity. In contrast, no hepatic effects or gall bladder lesions were found in B6C3F₁ mice ingesting ≤ 694 mg/kg/day (males) and $\leq 1,306$ mg/kg/day (females) 2-butoxy-ethanol in the drinking water for 13 weeks (NTP 1993). Furthermore, no adverse effects on liver weight or histopathology in the liver were noted in Swiss CD-1 male and female mice dosed with 1,300 mg/kg/day 2-butoxyethanol in the drinking water for 25 weeks (Heindel et al. 1990). However, the low- and high-dose mice (700 and 2,000 mg/kg/day, respectively) were not necropsied. When the offspring of these mice in the 700-mg/kg/day dose group were continued on the same treatment beginning at weaning and evaluated after 14 weeks, liver weight was significantly increased by 8% above the control value. Based on the LOAEL of 69 mg/kg/day for hepatic effects in male rats in the 13-week drinking study by NTP (1993), an intermediate oral MRL of 0.07 mg/kg/day was calculated as described in the footnote to Table 2-3 and in Appendix A.

Histological examination of the livers revealed no pathological lesions in male and female Wistar rats given unspecified acute oral doses of 2-butoxyethanol acetate in olive oil as part of a lethality study (Truhaut et al. 1979).

2. HEALTH EFFECTS

No histopathological lesions were found in the livers of male Alpk/AP (Wistar-derived) rats that were dosed once by gavage with 0, 174, 434, or 868 mg/kg 2-butoxyacetic acid (Foster et al. 1987).

Renal Effects. Intentional ingestion of 2-butoxyethanol by humans has been associated with renal toxicity. Renal failure was reported in an 87-year-old woman that died of cardiac arrest 3 days after ingesting an unknown amount of cleaner containing 6.5% 2-butoxyethanol (Litovitz et al. 1991). A male patient who was an abuser of alcohol and had a history of trichloroethylene ingestion was admitted to the hospital after ingesting 650 mg/kg 2-butoxyethanol contained in a household cleaning product; he exhibited slight albuminuria upon admission (Bauer et al. 1992). Similarly, a woman who ingested 467-933 mg/kg 2-butoxyethanol (also in window cleaner) developed oxahuria and a transient rise in serum creatinine (Rambourg-Schepens et al. 1988). Another female patient developed hematuria after ingesting 391-469 mg/kg 2-butoxyethanol, and also exhibited increased urinary excretion of oxalic acid, although within normal limits (Gijsenbergh et al. 1989). All three patients recovered after supportive therapy. In contrast, two children who accidentally ingested 290 or 1,862 mg/kg 2-butoxyethanol showed no adverse renal effects (Dean and Krenzelok 1992). Gastric emptying by administration of syrup of ipecac or by gastric lavage within minutes or hours of ingestion (time not specified) may have prevented any adverse effects. Renal effects were not observed in a man who ingested two doses (first dose, 1,006-1,341 mg/kg; second dose, 1,341 mg/kg) of a concentrated glass cleaner containing 2-butoxyethanol 12 days apart (Gualtieri et al. 1995). The details about how renal function was measured were not provided in this case report. After both doses, the man was treated with hemodialysis and ethanol; the treatment occurred within 8 hours of the second ingestion, but it is unclear from this report how much time elapsed between first ingestion and treatment and whether there might have been renal consequences had this treatment not taken place.

Renal effects, including hematuria, have been observed in animals after acute oral exposure to 2-butoxyethanol. Severely congested kidneys have been observed in rats that died after gavage doses of ≥ 530 mg/kg (Carpenter et al. 1956). Dark and/or enlarged kidneys were observed in male Wistar rats that received one dose of 1,310 mg/kg. Hematuria was observed in Wistar rats that received one dose of 2,560 or 5,000 mg/kg (Olin 1976) or $\geq 2,255$ mg/kg in rats that died (Union Carbide 1980b). Hematuria was also observed in an unspecified strain of rats given 500 or 1,000 mg/kg, but not 250 mg/kg, by gavage (Dow 1959) and in female Sprague-Dawley rats given 500 mg/kg (Sivarao and Mehendale 1995). Young (4-5 weeks) and adult (9-13 weeks) male Fischer 344 rats were dosed with 0, 32, 63, 125, 250, or 500 mg/kg 2-butoxyethanol by gavage; animals were killed at 24 and 48 hours after treatment and the kidneys were weighed, fixed, and examined histologically (Ghanayem et al. 1987a). Histopathological results were presented for the control,

2. HEALTH EFFECTS

125-, 250-, and 500-mg/kg dose groups. Secondary to the hemolytic effects, 2-butoxyethanol also caused histopathologic changes in the kidney, consisting of hemoglobin casts in the proximal tubules in 100% of the mature rats at ≥ 125 mg/kg; no effects were seen in young (4-5 weeks old) rats even at 500 mg/kg. The effects on the kidney in the mature rats were more severe at 24 hours after treatment and showed some recovery at 48 hours after treatment. Thus, this effect of 2-butoxyethanol was age-, dose-, and time-dependent, with older rats being more sensitive. Male Fischer 344 rats receiving 500 mg/kg 2-butoxyethanol by gavage exhibited similar effects in the kidney (Ghanayem et al. 1987b).

Pregnant Fischer 344 rats exhibited urethral bleeding, which may represent hematuria, after oral dosing by gavage in a preliminary teratology study at 600 mg/kg/day (but not at ≤ 300 mg/kg/day) 2-butoxyethanol on gestational days 9-11 or 11-13 (NTP 1989). In the definitive study, no kidney effects were noted at doses up to 200 mg/kg/day on gestational days 9-11 or 300 mg/kg/day on gestational days 11-13 (NTP 1989).

Increased kidney weight has been observed in animals after acute oral exposure to 2-butoxyethanol. Male rats were given 2-butoxyethanol orally for 4 consecutive days at 500 or 1,000 mg/kg/day (Grant et al. 1985). Animals were killed on days 1, 4, 8, and 22 after the final treatment. Increased kidney weight was observed at the high dose, but histological examination of the kidneys revealed no pathological lesions. No effects on kidney weight and no gross pathological lesions in the kidney were seen in Fischer 344 rats at ≤ 346 mg/kg/day (males) or ≤ 265 mg/kg/day (females) or in B6C3F₁ mice at ≤ 627 mg/kg/day (males) or $\leq 1,364$ mg/kg/day (females) in drinking water for 2 weeks (NTP 1993).

Renal effects have also been observed in animals after intermediate-duration oral exposure to 2-butoxyethanol. An unspecified, but statistically significant, increase in relative kidney weight was observed in Sherman rats at a dose of 1,540 mg/kg/day in the diet for 90 days (Carpenter et al. 1956). In DW Albino rats treated with 2-butoxyethanol in the diet for 91-93 days, relative kidney weights were increased by 18% in males at 919 mg/kg/day and 23% in females at 976 mg/kg/day (Weil and Carpenter 1963). This effect may have been associated with decreases in body weight gain and food consumption. No effects on kidney weight were noted at lower doses (188 mg/kg/day males, 222 mg/kg/day females), nor were any histopathological changes observed at any dose. No dose-related effects of treatment on kidney weight and no histopathological lesions in the kidney were observed in Sprague-Dawley rats at ≤ 506 mg/kg/day (males) and ≤ 444 mg/kg/day (females) 2-butoxyethanol in the drinking water for 21 days (Exon et al. 1991). After a 6-week exposure to 222, 443, or 885 mg/kg/day 2-butoxyethanol by gavage, male COBS CD (SD)BR rats

2. HEALTH EFFECTS

exhibited focal hemosiderin accumulation in the proximal tubules at 443 and 885 mg/kg/day (Eastman Kodak 1983; Krasavage 1986).

In Fischer 344 rats exposed to 2-butoxyethanol in the drinking water for 13 weeks, no treatment-related effects on kidney weight were observed (NTP 1993). Clinical chemistry and urinalysis revealed increases in blood urea nitrogen in males at ≥ 69 mg/kg/day at week 3 and at ≥ 281 mg/kg/day at week 13 and in females at ≥ 304 mg/kg/day at week 3 and ≥ 151 mg/kg/day at week 13; increases in blood creatinine in females at ≥ 304 mg/kg/day at week 13; decreases in total blood protein in males at ≥ 281 mg/kg/day at week 13 and in females at ≥ 151 mg/kg/day at weeks 3 and 13; decreases in blood albumin in males at ≥ 281 mg/kg/day at week 13 and in females at ≥ 363 mg/kg/day at week 3 and at ≥ 304 mg/kg/day at week 13; decreased urine volume in females at ≥ 82 mg/kg/day at week 13; and increased specific gravity of the urine in males at ≥ 69 mg/kg/day and in females at ≥ 151 mg/kg/day at week 13. Histological examination of the kidneys and urinary bladders of the rats revealed no pathological lesions. No renal effects (including no effects on kidney weight or clinical chemistry and urinalysis parameters, and no histopathological lesions in the kidney or urinary bladder) were found in B6C3F₁ mice in the same study at ≤ 694 mg/kg/day (males) and $\leq 1,306$ mg/kg/day (females) 2-butoxyethanol in the drinking water for 13 weeks (NTP 1993). However, an increase in kidney weight, although with no histopathological kidney lesions, was observed at 1,300 mg/kg/day in a reproductive toxicity study in which Swiss mice were given 2-butoxyethanol in the drinking water for 25 weeks; animals from the low- and high-dose groups (700 and 2,000 mg/kg/day) were not necropsied (Heindel et al. 1990). When the offspring of these mice in the 700-mg/kg/day dose group were continued on the same treatment beginning at weaning and evaluated after 14 weeks, there was also an increase in kidney weight.

Male and female Wistar rats given unspecified acute oral doses of 2-butoxyethanol acetate in olive oil as part of a lethality study exhibited renal effects including hematuria, tubular nephrosis, cloudy swelling of cells, dilatation of the proximal and distal convoluted tubules, and acute inflammation of the interstitial tissue (Truhaut et al. 1979).

In Alpk/AP (Wistar-derived) rats dosed once by gavage with 0, 174, 434, or 868 mg/kg 2-butoxyacetic acid, hematuria was noted at 868 mg/kg but not at the lower doses (Foster et al. 1987).

Endocrine Effects. Very few data are available to describe endocrine effects of 2-butoxyethanol by oral exposure. Wistar rats exhibited red adrenal glands, which may be related to the hemolytic effects of

2. HEALTH EFFECTS

2-butoxyethanol, at necropsy after single gavage doses of 2,255-9,019 mg/kg (Union Carbide 1980b). It should be noted that two of five rats treated with 2,255 mg/kg and all rats treated with higher doses died. Male COBS CD (SD)BR rats showed no histopathologic changes in pancreas, adrenal glands, pituitary, thyroid, or parathyroid after oral exposure to doses of ≤ 885 mg/kg/day 2-butoxyethanol for 6 weeks, 5 days per week (Eastman Kodak 1983; Krasavage 1986). No adverse histological effects were noted in the adrenal glands, pancreas, thyroid, or parathyroid of DW Albino rats fed 2-butoxyethanol in the diet for 91-93 days at doses up to 919 mg/kg/day for males and 976 mg/kg/day for females (Weil and Carpenter 1963). No adverse histopathological effects on endocrine glands (including adrenal, pancreas, parathyroid, pituitary, and thyroid) were noted in Fischer 344 rats at ≤ 452 mg/kg/day (males) and 1470 mg/kg/day (females) or in B6C3F₁ mice at ≤ 694 mg/kg/day (males) and $\leq 1,306$ mg/kg/day (females) (NTP 1993).

Male and female Wistar rats given unspecified acute oral doses of 2-butoxyethanol acetate in olive oil as part of a lethality study exhibited no histopathological changes in the pancreas or adrenal glands (Truhaut et al. 1979).

Dermal Effects. Female Fischer 344 rats exhibited rough hair coats and necrosis of the tail after a single dose of 1,000 mg/kg 2-butoxyethanol (Dow 1981). Necrosis of the tail tip may have been a vascular response to the toxic effects of 2-butoxyethanol on red blood cells. Rough coat was also observed in rats that died after receiving ≥ 530 mg/kg (Carpenter et al. 1956). Male Wistar rats exhibited piloerection after single doses of $\geq 1,310$ mg/kg of 2-butoxyethanol by gavage (Olin 1976). Pregnant Fischer 344 rats exhibited pale coloration after oral dosing in a preliminary teratology study with 600 mg/kg/day 2-butoxyethanol on gestational days 9-11 or 11-13 (NTP 1989). In the definitive study, no dermal effects were noted at ≤ 200 mg/kg/day on gestational days 9-11 or ≤ 300 mg/kg/day on gestational days 11-13 (NTP 1989). Histological examination of skin revealed no treatment-related dermal lesions in Fischer 344 rats at ≤ 452 mg/kg/day (males) and ≤ 470 mg/kg/day (females) or in B6C3F₁ mice at ≤ 694 mg/kg/day (males) and $\leq 1,306$ mg/kg/day (females) in drinking water for 13 weeks (NTP 1993).

Ocular Effects. A woman who ingested 391-469 mg/kg 2-butoxyethanol exhibited isoco& light reactive mydriasis upon admission to the hospital (Cijssenbergh et al. 1989). This resolved quickly after supportive therapy.

Female Fischer 344 rats exhibited palpebral closure after a single gavage dose of 2,000 mg/kg 2-butoxyethanol, a dose which resulted in the death of 2 of 3 rats (Dow 1981). Pregnant Fischer 344 rats exhibited

2. HEALTH EFFECTS

chromodacryorrhea after oral dosing in a preliminary teratology study with 600 mg/kg/day 2-butoxyethanol on gestational days 9-11 or 11-13 (NTP 1989). In the definitive study, no ocular effects were noted at ≤ 200 mg/kg/day on gestational days 9-11 or ≤ 300 mg/kg/day on gestational days 11-13 (NTP 1989). Histological examination of the eyes revealed no pathological lesions in male COBS CD (SD)BR rats dosed by gavage with ≤ 885 mg/kg/day 2-butoxyethanol for 6 weeks (Eastman Kodak 1983; Krasavage 1986), in Fischer 344 rats given 2-butoxyethanol in drinking water at ≤ 452 mg/kg/day (males) and ≤ 470 mg/kg/day (females) for 13 weeks, or in B6C3F₁ mice given 2-butoxyethanol in drinking water at ≥ 694 mg/kg/day (males) and $\leq 1,306$ mg/kg/day (females) for 13 weeks (NTP 1993).

Body Weight Effects. Reduced body weight has been observed in animals after acute oral exposure to 2-butoxyethanol. While female Fischer 344 rats given single gavage doses of 2-butoxyethanol $\leq 2,000$ mg/kg were reported to gain weight during the post-treatment observation period, no controls were used for comparison (Dow 1981). Guinea pigs treated with a single gavage dose of 500, 1,000 or 2,000 mg/kg 2-butoxyethanol were reported to gain weight during a 14-day observation period (Shepard 1994b), but no controls were used in this study. In male Fischer 344 rats, a gavage dose of 1,000 mg/kg/day for 4 days resulted in reduced body weight gain compared with controls (Grant et al. 1985). No effect on body weight was seen in male Fischer 344 rats that received 2-butoxyethanol in drinking water at ≤ 346 mg/kg/day for 2 weeks, but the female rats displayed a decrease in body weight gain during exposure and decreased final body weight at 265 mg/kg/day but not at ≤ 203 mg/kg/day (NTP 1993). The decrease in body weight gain may have been related to decreased water consumption. Male Swiss mice lost 31% of their initial body weight at 12,750 mg/kg/day 2-butoxyethanol administered in the drinking water for 2 weeks (Heindel et al. 1990). No weight loss was observed in the male mice at $\leq 2,550$ mg/kg/day. The female mice were reported to respond similarly, but the degree of weight loss and the doses associated with the weight loss were not reported. No effect on body weight was observed in B6C3F₁ mice at ≤ 627 mg/kg/day (males) and $\leq 1,364$ mg/kg/day (females) of 2-butoxyethanol in the drinking water for 2 weeks (NTP 1993).

Pregnant Fischer 344 rats exhibited decreased gestational weight gain in a preliminary teratology study at ≥ 150 mg/kg/day 2-butoxyethanol on gestational days 9-11 or 11-13 (NTP 1989). The decreased gestational weight gain may have been related to decreases in food and water intake. In the definitive study, gestational weight gain was reduced at 200 mg/kg/day in the pregnant rats treated on gestational days 9-11 and at 300 mg/kg/day in the pregnant rats treated on gestational days 11-13 (NTP 1989). The decreased gestational weight gain may have been related to decreases in food and water intake. In a developmental study in which pregnant CD-1 mice were given 0, 350, 650, 1,000, 1,500, or 2,000 mg/kg/day 2-butoxy-

2. HEALTH EFFECTS

ethanol by gavage on gestational days 8-14 to determine prenatal responses, or 0, 650, or 1,000 mg/kg/day on gestational days 8-14 to determine postnatal responses, unspecified decreases in maternal body weight gain were reported at 2,000 mg/kg/day in the prenatal experiment and at 1,000 mg/kg/day in the postnatal experiment (Wier et al. 1987). Similarly, in another developmental study, pregnant CD-1 mice given a dose of 1,180 mg/kg/day on gestational days 6-13 exhibited an 80% decrease in body weight gain (Hardin et al. 1987; Schuler et al. 1984).

Effects on body weight have also been observed in animals exposed orally to 2-butoxyethanol for intermediate durations. An unspecified decrease in body weight gain was reported for Sherman rats that received 1,540 mg/kg/day in drinking water for 90 days (Carpenter et al. 1956). In DW Albino rats treated with 2-butoxyethanol in the diet for 91-93 days, body weight gain was decreased by 53% in males at 919 mg/kg/day, and 45% in females at 976 mg/kg/day (Weil and Carpenter 1963). Body weight gain was decreased by as much as 91% at day 1 of the study (on day 1) in males at 188 mg/kg/day, but was only 9% lower than controls by the end of the study. The 188-mg/kg/day dose in males, and the 976-mg/kg/day dose in females, was also associated with about an 18% decrease in food intake. No effects on body weight gain were noted at 28 mg/kg/day in males and 222 mg/kg/day in females. Decreased body weight gain in the presence of reduced food consumption occurred in male COBS CD (SD)BR rats given 885 mg/kg/day by gavage for 6 weeks (Eastman Kodak 1983; Krasavage 1986). While no effect on body weight was observed in Sprague-Dawley rats given ≤ 506 mg/kg/day (males) and ≤ 444 mg/kg/day (females) in drinking water for 21 days (Exon et al. 1991), decreased body weight gain was noted in male Fischer 344 rats treated for 60 days at 443 mg/kg/day 2-butoxyethanol and in Fischer 344 rats treated for 13 weeks at ≥ 367 mg/kg/day (males) and ≥ 363 mg/kg/day (females) with 2-butoxyethanol in drinking water (NTP 1993). The decreased body weight gain may have been related to decreased water consumption.

Swiss mice that were exposed to 0, 700, 1,300, or 2,100 mg/kg/day 2-butoxyethanol in the drinking water for 25 weeks exhibited decreased terminal body (at the end of the 25 week treatment period) weight at 1,300 mg/kg/day in females but not in males; the low- and high-dose groups were not evaluated (Heindel et al. 1990). The decreased body weight may have been related to decreased water consumption. When the offspring of these mice in the 700-mg/kg/day dose group were continued on the same treatment beginning at weaning and evaluated after 14 weeks, there was no effect on body weight. No effect on body weight was observed in B6C3F₁ mice at ≤ 694 mg/kg/day (males) or $\leq 1,306$ mg/kg/day (females) 2-butoxyethanol in drinking water for 13 weeks (NTP 1993).

2. HEALTH EFFECTS

Groups of male Alpk/AP (Wistar-derived) rats were dosed once by gavage with 0, 174, 434, or 868 mg/kg 2-butoxyacetic acid (Foster et al. 1987). Body weight gain was decreased during the first 2 days after treatment at all doses, but returned to normal by day 14.

Metabolic Effects. Metabolic acidosis was reported in an 87-year-old woman who died of cardiac arrest 3 days after she ingested an unknown amount of a cleaner containing 6.5% 2-butoxyethanol (Litovitz et al. 1991). Ethylene glycol levels were 110 mg/dL in this patient shortly after hospital admission and 10 mg/dL 3 days later. A male patient, who had a history of alcohol and trichloroethylene abuse, was admitted to the hospital after ingestion of 500 mL of a household cleaning fluid containing 2-butoxyethanol, which was equivalent to a dose of 650 mg/kg (Bauer et al. 1992). Metabolic acidosis and hypoxemia with lactic acidosis were observed. In other case reports, a woman admitted to the hospital after ingesting 250-500 mL of a window cleaner containing 12% (467-933 mg/kg) 2-butoxyethanol developed metabolic acidosis and hypokalemia (Rambourg-Schepens et al. 1988) and a woman ingesting 391-469 mg/kg 2-butoxyethanol developed metabolic acidosis (Gijzenbergh et al. 1989). Significant acid-base disturbance, not described further in this case report, was observed in a man following ingestion of 1,006-1,341 mg/kg 2-butoxyethanol in a concentrated glass cleaner (Gualtieri et al. 1995). A second ingestion of the glass cleaner (1,341 mg/kg 2-butoxyethanol) 12 days later did not result in metabolic disturbances. After both doses, the man was treated with hemodialysis and ethanol; the treatment occurred within 8 hours of the second ingestion, but it is unclear from this report how much time elapsed between the first ingestion and treatment and how the treatment affected the observed outcome. Two children who ingested 290 or 1,862 mg/kg 2-butoxyethanol did not exhibit evidence of metabolic acidosis during a 24-hour observation period following gastric emptying (Dean and Krenzelok 1992). Metabolic acidosis is likely due to the formation of butoxyacetic acid from 2-butoxyethanol (see section 2.3.3 Metabolism).

Other Systemic Effects. Decreased water consumption was seen in Fischer 344 rats ingesting 2-butoxyethanol at ≥ 152 mg/kg/day (females) and ≥ 242 mg/kg/day (males) in drinking water for 2 weeks (NTP 1993). In B6C3Fr mice treated similarly, decreased water consumption was seen in female mice at ≥ 150 mg/kg/day. In the same study, male mice receiving ≥ 370 mg/kg/day exhibited signs of dehydration. An unspecified decrease in fluid intake was reported for male and female Swiss mice at $\geq 1,275$ mg/kg/day of 2-butoxyethanol administered in drinking water for 2 weeks (Heindel et al. 1990).

Pregnant Fischer 344 rats exhibited decreased food and water intake at ≥ 150 mg/kg/day and were cold to the touch at 600 mg/kg/day after gavage dosing in a preliminary teratology study with 2-butoxyethanol on

2. HEALTH EFFECTS

gestational days 9-11 or 11-13 (NTP 1989). In the definitive study, decreased food and water intake were noted at doses of 200 mg/kg/day on gestational days 9-11 or 300 mg/kg/day on gestational days 11-13 (NTP 1989).

Sprague-Dawley rats given ≤ 506 mg/kg/day 2-butoxyethanol in drinking water for 21 days exhibited decreased water consumption at the high dose (506 mg/kg/day for males and 444 mg/kg/day for females) (Exon et al. 1991). In male COBS CD (SD)BR rats, 885 mg/kg/day 2-butoxyethanol administered by gavage for 6 weeks caused decreased food consumption (Eastman Kodak 1983; Krasavage 1986). In Fischer 344 rats given 2-butoxyethanol in drinking water for 13 weeks, decreased water consumption was observed at ≥ 129 mg/kg/day (males) and ≥ 151 mg/kg/day (females) (NTP 1993). In B6C3F₁ mice similarly exposed at ≤ 694 mg/kg/day (males) and $\geq 1,306$ mg/kg/day (females), average water consumption was variable, and no clear treatment-related patterns were evident. However, an unspecified decrease in water consumption was reported for male and female Swiss mice at 700 mg/kg/day 2-butoxyethanol administered in drinking water for up to 25 weeks (Heindel et al. 1990). Decreased food intake was observed DW albino rats treated with 2-butoxyethanol in the diet (Weil and Carpenter 1963). Food intake was about 18% lower than controls in males fed 188 mg/kg/day and 23% lower than controls in females fed 976 mg/kg/day. No effects on food intake were observed at 28 mg/kg/day in males or at 222 mg/kg/day in females.

Staining of the perineal region was observed in female Fischer 344 rats given single gavage doses of ≥ 130 mg/kg 2-butoxyethanol (Dow 1981). In a developmental study, in which pregnant CD-1 mice were given 350, 650, 1,000, 1,500, or 2,000 mg/kg/day on gestational days 8-14, a green-brown or red-brown staining of cage papers was observed at ≥ 650 mg/kg/day (Wier et al. 1987). At 1,500 and 2,000 mg/kg/day, green or red vaginal discharge was also observed. These effects were most likely the result of hematuria, hemoglobinuria, or vaginal bleeding (see Section 2.2.2.5), although the investigators did not draw this conclusion in their publications.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after oral exposure to 2-butoxyethanol or 2-butoxyethanol acetate. No studies were located regarding immunological effects in animals after oral exposure to 2-butoxyethanol acetate. No studies were located regarding immunological or lymphoreticular effects in animals or humans after oral exposure to 2-butoxyacetic acid.

2. HEALTH EFFECTS

Information on immunological effects of 2-butoxyethanol in animals exposed orally to 2-butoxyethanol is limited to one acute and one intermediate study. Male Fischer 344 rats were immunized with trinitrophenyl-lipopolysaccharide (TNP-LPS) and then dosed by gavage (4 and 28 hours after immunization) to 0, 50, 100, 200, or 400 mg/kg/day 2-butoxyethanol in distilled water for 2 consecutive days (Smialowicz et al. 1992). Three days later, the primary plaque-forming cell (PFC) response to TNP-LPS was determined. The PFC response to TNP-LPS was used to evaluate B-lymphocyte antibody production. No toxic effect of 2-butoxyethanol in the immune system was detected. In Sprague-Dawley rats, in which males received doses of 180 or 506 mg/kg/day 2-butoxyethanol and females received doses of 204 or 444 mg/kg/day 2-butoxyethanol in the drinking water for 21 days, serum samples were analyzed for antibody levels to keyhole limpet hemocyanin (KLH), and spleens were used as the cell source to assess natural killer cell cytotoxicity and interleukin 2 and interferon production. In addition, the weights of thymus and spleen were determined and thymuses were examined histologically. For antigen presentation, KLH was injected subcutaneously in the base of the tail 7 days after the beginning of treatment with 2-butoxyethanol and again on day 13 to initiate an IgG antibody response. On day 20, KLH was injected into the right footpad to assess the 24-hour delayed-type hypersensitivity reaction by subtracting the thickness of the saline-injected left footpad from the thickness of the KLH-injected footpad. There was no effect of 2-butoxyethanol treatment on anti-KLH IgG antibody production and on delayed-type hypersensitivity reaction. Splenic natural killer cytotoxic responses, which were assessed by the 4-hour ^{51}Cr release from YAC-1 tumor target cells *in vitro* were significantly ($p \leq 0.05$) increased in both sexes at the low dose only. The increase in natural killer cytotoxic responses is not considered an adverse effect. There were no effects of 2-butoxyethanol treatment on splenocyte production of interleukin 2 and interferon, and thymus and spleen weights. No histological lesions in the thymus were observed.

Several acute oral studies have examined the effects of 2-butoxyethanol on lymphoreticular organs. In a preliminary teratology study, pregnant Fischer 344 rats treated by gavage with ≥ 150 mg/kg/day 2-butoxyethanol on gestational days 9-11 or 11-13 exhibited increased absolute spleen weight at all doses compared with controls (NTP 1989). In the definitive study, in which the doses were 30, 100, or 200 mg/kg/day on gestational days 9-11 and 30, 100, and 300 mg/kg/day on gestational days 11-13, increased absolute spleen weight was noted at a dose level of ≥ 100 mg/kg/day in both experiments (NTP 1989).

Young (4-5 weeks), adult (9-13 weeks) and older (5-16 months) male Fischer 344 rats were dosed with 0, 32, 63, 125, 250, or 500 mg/kg 2-butoxyethanol by gavage (Ghanayem et al. 1987a). Young and adult rats receiving ≥ 125 mg/kg exhibited a dose-related increase in relative spleen weight; at 125 mg/kg the increase

2. HEALTH EFFECTS

relative to control was 110% for young rats and 150% for adult rats. Spleen weights were not recorded for the older rats. Ghanayem and coworkers have published other results indicating similar effects in male Fischer 344 rats after a single dose of 125 or 500 mg/kg 2-butoxyethanol by gavage (Ghanayem et al. 1987b). Repeated dosing with 2-butoxyethanol seems to lessen the effect on the spleen weight increase. Male Fischer 344 rats received 0 or 125 mg/kg/day 2-butoxyethanol in water by gavage for 1, 2, 3, 6, or 12 consecutive days (Ghanayem et al. 1992). Treated animals showed a time-dependent increase in spleen weight which reached a maximum of 62% in 6 days and declined to 45% between days 6 and 12. In the same study, using a different study design, male Fischer 344 rats received 125 mg/kg/day 2-butoxyethanol in water by gavage for 3 consecutive days. Controls received 5 mL water/kg body weight daily for 3 consecutive days. Rats in both groups were then allowed to recover without treatment for 7 days. These rats were then subgrouped with control and pretreated animals in each subgroup, and treated with water, 125 mg/kg, or 250 mg/kg 2-butoxyethanol. Twenty-four hours after dosing, the spleen was removed and weighed. Pretreatment with 2-butoxyethanol resulted in a smaller increase in spleen weight than was observed in the rats that were not pretreated. Male Fischer 344 rats given 2-butoxyethanol orally for 4 consecutive days at 500 or 1,000 mg/kg/day exhibited increased spleen weight and extramedullary hematopoiesis (Grant et al. 1985).

No effects on absolute or relative thymus weight were observed in Fischer 344 rats given 2-butoxyethanol at ≤ 346 mg/kg/day (males) and ≤ 265 mg/kg/day (females) in the drinking water for 2 weeks (NTP 1993). However, male B6C3F₁ mice exhibited a 38% decrease in absolute thymus weight and a 39% decrease in relative thymus weight after treatment with 370 mg/kg/day, and a 20% decrease in absolute thymus weight and a 23% decrease in relative thymus weight at 627 mg/kg/day 2-butoxyethanol in the drinking water for 2 weeks, but females dosed at $\leq 1,364$ mg/kg/day showed no effect on thymus weight (NTP 1993).

Effects on lymphoreticular organs have also been examined in intermediate-duration oral studies. Increased spleen weights were found at ≥ 443 mg/kg/day in male CQBS CD (SD)BR rats treated by gavage with 2-butoxyethanol for 6 weeks (Eastman Kodak 1983; Krasavage 1986). Enlarged dark spleens were observed in three of nine rats exposed at 443 mg/kg/day and in four of eight rats at 885 mg/kg/day. Splenic congestion secondary to the hematological effects was seen at all doses (≥ 222 mg/kg/day). Histological examination of the thymus, mesenteric lymph nodes, and bone marrow revealed no pathological lesions, and no effect on white blood cells was noted. In Fischer 344 rats exposed to 2-butoxyethanol in drinking water for 13 weeks, bone marrow hyperplasia was found in males at ≥ 281 mg/kg/day and in females at ≥ 363 mg/kg/day; hematopoietic cell proliferation and congestion in the spleen were found in males at ≥ 367 mg/kg/day and in

2. HEALTH EFFECTS

females at ≥ 363 mg/kg/day; increased hemosiderin pigmentation in the spleen was found in males at ≥ 129 mg/kg/day and in females at ≥ 151 mg/kg/day (NTP 1993). The absolute thymus weight was decreased in males at ≥ 367 mg/kg/day and in females at 470 mg/kg/day. No histopathological lesions were found in the thymus or lymph nodes. In contrast to rats, B6C3F₁ mice receiving ≤ 694 mg/kg/day (males) and $\leq 1,306$ mg/kg/day (females) for 13 weeks in the drinking water showed no effect on thymus weight and no gross or histopathological lesion in the spleen, thymus, lymph nodes, or bone marrow (NTP 1993). No effect on thymus or spleen weight, and no histopathological lesions in the thymus were observed in rats given < 506 mg/kg/day for 21 days (Exon et al. 1991).

In a study on 2-butoxyethanol acetate, Wistar rats given unspecified acute oral doses of 2-butoxyethanol acetate in olive oil as part of a lethality study exhibited no histopathological changes in the spleen (Truhaut et al. 1979).

Spleen weight effects, spleen congestion, spleen and bone marrow hematopoiesis, and hemosiderin pigmentation in the spleen are probably related to hemolytic effects of 2-butoxyethanol, which are discussed in Section 2.2.2.2 under Hematological Effects

The highest NOAEL values and all LOAEL values from each reliable study for immunological and lymphoreticular effects in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to 2-butoxyethanol acetate or 2-butoxyacetic acid or in animals after oral exposure to 2-butoxyacetic acid.

Intentional poisoning with 2-butoxyethanol has been associated with neurological effects. A woman who died of cardiac arrest 3 days after she ingested an unspecified amount of cleaner containing 6.5% 2-butoxyethanol was comatose upon admission to the hospital (Litovitz et al. 1991). A male patient, who was a known alcohol and trichloroethylene abuser, was comatose upon admission to the hospital after ingesting a household cleaning fluid that provided a dose of about 650 mg/kg 2-butoxyethanol (Bauer et al. 1992). Similarly, a woman who ingested 467-933 mg/kg 2-butoxyethanol (also in window cleaner) was in a coma with no response to painful stimuli (Rambourg-Schepens et al. 1988), and another woman who ingested

2. HEALTH EFFECTS

391-469 mg/kg 2-butoxyethanol became comatose (Gijsenbergh et al. 1989). All three patients recovered after supportive therapy. In contrast, no signs of neurological effects were seen in two children who accidentally ingested 270 or 1,862 mg/kg 2-butoxyethanol and who were observed for 24 hours after gastric lavage (Dean and Krenzelok 1992).

Clinical signs of neurotoxicity have also been observed in animals after acute oral exposure to 2-butoxyethanol. Rats that died after a single gavage dose of ≥ 530 mg/kg exhibited sluggishness, prostration, and narcosis (Carpenter et al. 1956). Other investigators have reported drowsiness, sluggishness, lethargy, muscular flaccidity, and/or ataxia after acute exposure of rats to 252-9,000 mg/kg/day (Dow 1959, 1981; Eastman Kodak 1983; Krasavage 1986; Olin 1976; Sivarao and Mehendale 1995; Union Carbide 1980b). Moderate-to-severe weakness and prostration were observed directly after dosing in guinea pigs given a single gavage dose of 1,000 mg/kg 2-butoxyethanol, a dose that resulted in the death of 1 of 5 males and 1 of 5 females (Shepard 1994b). Slight weakness was observed directly after dosing at 500 mg/kg, a dose at which all treated guinea pigs survived. Pregnant Fischer 344 rats exhibited lethargy after oral dosing in a preliminary teratology study with 600 mg/kg/day 2-butoxyethanol given by gavage on gestational days 9-11 or 11-13 (NTP 1989). In the definitive study, no adverse neurological clinical signs were noted at ≤ 200 mg/kg/day on gestational days 9-11 or ≤ 300 mg/kg/day on gestational days 11-13 (NTP 1989). Pregnant CD-1 mice given doses of 1,500 or 2,000 mg/kg/day 2-butoxyethanol by gavage on gestational days 8-14 exhibited lethargy and failure to right when turned over, but no effect on demeanor was seen at $\leq 1,000$ mg/kg/day (Wier et al. 1987).

Adult male COBS CD (SD)BR rats were given undiluted 2-butoxyethanol by gavage in doses of 0, 222, 443, or 885 mg/kg/day, 5 days per week over a 6-week period, and exhibited lethargy at ≥ 443 mg/kg/day after the first dose (Eastman Kodak 1983; Krasavage 1986). The high-dose rats were slightly weak and inactive after the second and third doses. No effect on absolute brain weight was observed, but relative brain weight was increased at ≥ 443 mg/kg/day. No histopathological changes were seen in brain tissue at any dose. Fischer 344 rats that received 2-butoxyethanol at ≤ 452 mg/kg/day (males) and ≤ 470 mg/kg/day (females) and B6C3F₁ mice that received ≤ 694 mg/kg/day (males) and $\leq 1,306$ mg/kg/day (females) in the drinking water for 13 weeks showed no adverse effects on demeanor or histopathological changes in brain, spinal cord, or sciatic nerve (NTP 1993).

2. HEALTH EFFECTS

Wistar rats given unspecified acute oral doses of 2-butoxyethanol acetate in olive oil as part of a lethality study exhibited no adverse neurological clinical signs or histopathological changes in the brain (Truhaut et al. 1979).

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to 2-butoxyethanol, 2-butoxyethanol acetate, or 2-butoxyacetic acid.

In acute studies, no effects on testicular weight and no histopathological effects in the testes were found in male Fischer 344 rats given 2-butoxyethanol orally once at ≤ 500 mg/kg (Ghanayem et al. 1987a) or for 4 consecutive days at 500 or 1,000 mg/kg/day (Grant et al. 1985). Likewise, no effects on testicular weight and no histopathological lesions in the testes or epididymides were found in Fischer 344 rats at ≤ 346 mg/kg/day or in B6C3F₁ mice at ≤ 627 mg/kg/day 2-butoxyethanol in drinking water for 2 weeks (NTP 1993).

In intermediate-duration studies, no effects on testicular weight and no histopathological lesions in the testes were found in Sprague-Dawley rats at ≤ 506 mg/kg/day 2-butoxyethanol for 21 days (Exon et al. 1991). No effects on testicular weight and no histopathological lesions in the testes, seminal vesicles, epididymides, or prostate were found in COBS CD (SD)BR rats treated by gavage at ≤ 885 mg/kg/day for 6 weeks (Eastman Kodak 1983; Krasavage 1986). No effects on testicular weight and no histopathological lesions in the testes or epididymides (or seminal vesicles in the 13-week study) were found in Fischer 344 rats given ≤ 443 mg/kg/day in the drinking water for 60 days or ≤ 452 mg/kg/day in the drinking water for 13 weeks (NTP 1993). Although spermatozoa concentrations (10^6 /g caudal epididymal tissue) were significantly ($p \leq 0.01$) decreased compared to controls at ≥ 281 mg/kg/day, a dose-related effect was not observed (control, 713.9 ± 16.2 ; 281 mg/kg/day, 633.0 ± 13.1 ; 367 mg/kg/day, 656.3 ± 13.3 ; 452 mg/kg/day, 617.2 ± 22.9), and there were no significant effects on spermatid heads (10^7 /g testes or 10^7 /testis), spermatid counts (mean/ 10^4 mL), or percent mobile spermatozoa. A small, older study (Weil and Carpenter 1963) did find histological evidence of testicular atrophy after 93 days exposure to 188 mg/kg/day in DW albino rats.

2. HEALTH EFFECTS

No effects on the weights of testes/seminal vesicles and coagulating gland and no histopathological lesions in these tissues were found in JCL-ICR mice treated by gavage at 1,000 mg/kg/day for 5 weeks (Nagano et al. 1979, 1984). No significant effects on the weights of testes, seminal vesicles, or prostate and no effects on sperm parameters were found in Swiss mice in a continuous breeding drinking water study at 1,300 mg/kg/day or in the male offspring at 700 mg/kg/day (Heindel et al. 1990). Slight but statistically significant ($p \leq 0.01$) decreases in left testis, but not right testis, weights were observed in B6C3F₁ mice at ≥ 210 mg/kg/day in drinking water for 13 weeks (NTP 1993). Because the effect on left testis weight was not dose-related (and there were no effects on right testis weight), it was not considered biologically significant. In addition, no histopathological changes were observed in the seminal vesicles or testes/epididymides, nor were there any consistent treatment-related effects on sperm parameters in mice at ≤ 627 mg/kg/day in drinking water for 13 weeks (NTP 1993).

Female Fischer 344 rats treated with 2-butoxyethanol in the drinking water for 13 weeks exhibited altered estrous cycles at ≥ 363 mg/kg/day, with more time spent in diestrus than in the other phases (NTP 1993). The total duration of the estrous cycle was not affected. No histopathological lesions were found in the mammary glands, ovaries, or uterus. No effect on estrous cycles and no histopathological lesions in the mammary glands, ovaries, or uterus were found in female B6C3F₁ mice similarly treated for 13 weeks at $\leq 1,306$ mg/kg/day (NTP 1993).

Pregnant Fischer 344 rats exhibited vaginal bleeding after oral dosing by gavage in a preliminary teratology study with 600 mg/kg/day 2-butoxyethanol on gestational days 9-11 or 11-13 (NTP 1989). In the definitive study, increased resorptions, implantation loss, and vaginal bleeding were noted at the high doses of 200 mg/kg/day on gestational days 9-11 and 300 mg/kg/day on gestational days 11-13 (NTP 1989). These doses were also maternally toxic. A decrease in the incidence of viable litters was found in pregnant CD-1 mice treated with 1,180 mg/kg/day by gavage on gestational days 6-13, a dose that resulted in decreased maternal body weight gain (Hardin et al. 1987; Schuler et al. 1984). Pregnant female CD-1 mice given 350-2,000 mg/kg/day 2-butoxyethanol on gestational days 8-14 exhibited a green or red vaginal discharge during gestation at doses of 1,500 and 2,000 mg/kg/day; surviving animals in the 1,000- and - 1,500-mg/kg/day dose groups had an increased incidence of resorptions (Wier et al. 1987).

Mating pairs of Swiss mice exposed to 1,300 or 2,100 mg/kg/day 2-butoxyethanol in the drinking water for 21 weeks exhibited a decrease in the number of litters produced per pair, and in the size of each litter, with decreased pup weight. However, the low dose, 700 mg/kg/day, produced no adverse effect on fertility

2. HEALTH EFFECTS

(Heindel et al. 1990). When the females that had been dosed with 1,300 mg/kg/day 2-butoxyethanol were mated with control males, and then maintained on treatment throughout gestation to delivery, they produced 58% fewer litters, and the litters were 66% smaller compared to control mating pairs. When the offspring of the low-dose mating pairs (700 mg/kg/day) were mated, there was no adverse effect on fertility. A few females in the treated group (1,300mg/kg/day) had long or unclear estrous cycles, but the significance of this is not clear (Heindel et al. 1990).

Wistar rats given unspecified acute oral doses of 2-butoxyethanol acetate in olive oil as part of a lethality study exhibited no adverse histopathological changes in the testes or ovaries (Truhaut et al. 1979).

Groups of male Alpk/AP (Wistar-derived) rats were dosed once by gavage with 0, 174, 434, or 868 mg/kg 2-butoxyacetic acid (Foster et al. 1987). Occasional significant decreases in the weight of the prostate and seminal vesicles were observed, but the decreases were not time or dose related. Histological examination of testes, epididymides, and prostate revealed no treatment-related lesions.

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Tables 2-3 and 2-5 and plotted in Figures 2-3 and 2-5.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to 2-butoxyethanol, 2-butoxyethanol acetate, or 2-butoxyacetic acid. No studies were located regarding developmental effects in animals after oral exposure to 2-butoxyethanol acetate or 2-butoxyacetic acid.

The offspring of pregnant Fischer 344 rats exhibited decreased fetal body weight after oral dosing of the dams in a preliminary teratology study with 300 and 600 mg/kg/day 2-butoxyethanol on gestational days 9-11 (NTP 1989). Decreased gravid uterine weight and decreased fetal body weight were found at 600 mg/kg/day after dams were dosed on gestational days 11-13. However, no external or internal malformations were observed in the fetuses after the dams were treated with ≤ 600 mg/kg/day on gestational days 9-11 or 11-13. The doses that resulted in fetal effects also caused maternal toxicity. In the definitive study, no adverse developmental effects (fetal weight or external and visceral malformations) were noted at ≤ 200 mg/kg/day on gestational days 9-11 or ≤ 300 mg/kg/day on gestational days 11-13 (NTP 1989). CD-1 mice were treated by gavage with 1,180 mg/kg/day 2-butoxyethanol on gestational days 6-13 and allowed to

2. HEALTH EFFECTS

litter (Hardin et al. 1987; Schuler et al. 1984). As noted in Section 2.2.2.5 above, treated females had significantly reduced numbers of viable litters, but no adverse effects were observed in the pups that were born alive. However, the offspring of pregnant female CD-1 mice given 1,000 or 1,500 mg/kg/day 2-butoxyethanol on gestational days 8-14 exhibited evidence of cleft palate when evaluated at term (Wier et al. 1987). The response was not clearly dose related; one of five litters (4/43 fetuses) and one of three litters (1/25 fetuses) were affected at 1,000 and 1,500 mg/kg/day, respectively. The 1,000-mg/kg/day dose was associated with green-brown or red-brown staining of the cage papers, while at 1,500 mg/kg/day three of six mice died. In a postnatal study designed to examine pup survival beyond the neonatal period, cleft palate effect was not evident when mice dosed with 650 or 1,000 mg/kg/day (Wier et al. 1987). In a reproductive toxicity study, male and female Swiss mice were given doses of 700, 1,300, or 2,100 mg/kg/day in drinking water for 21 weeks (Heindel et al. 1990). Decreased pup weight was observed for all treated mating pairs at ≥ 700 mg/kg/day. A crossover mating trial (performed to assess which sex had been affected by treatment, or which sex is more affected) indicated that the reproductive effects could be attributed primarily to an effect on the female, although no developmental effects were observed in the offspring that were produced (Heindel et al. 1990). The crossover mating trial was performed after the last litter from the continuous breeding phase was weaned to determine the affected sex. The crossover mating trial consisted of 3 groups of 20 pairs each -- control males x control females, control males x high dose females, and control females x high dose males. Pairs were matched for 7 days or until a copulatory plug is detected, whichever is first. When the offspring of the 700-mg/kg/day animals were mated while being maintained on treatment from weaning throughout mating, gestation, and delivery (14 weeks), no developmental effects were observed in the pups (Heindel et al. 1990).

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 2-3 and plotted in Figure 2-3.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to 2-butoxyethanol, 2-butoxyethanol acetate, or 2-butoxyacetic acid. *In vitro* genotoxicity studies are discussed in Section 2.5.

2. HEALTH EFFECTS

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after oral exposure to 2-butoxyethanol, 2-butoxyethanol acetate, or 2-butoxyacetic acid.

2.2.3 Dermal Exposure

Occupational or environmental exposure to 2-butoxyethanol or 2-butoxyethanol acetate usually occurs through the inhalation or dermal route. Both routes of exposure are important in the industrial setting. Occupational exposure to 2-butoxyethanol usually involves co-exposure to other solvents and chemicals. In several NIOSH Health Hazard Evaluations, effects reported by workers included eye, nose, and throat irritation; coughing; runny nose; headache; dizziness; lightheadedness; and nausea (Apoll98 1,1986; Lee 1988). Since personal breathing zone and workplace air samples analyzed for solvents and other chemicals such as, toluene, xylene, methyl ethyl ketone, methyl isobutyl ketone, styrene, along with 2-butoxyethanol, indicated that exposure levels for each chemical were below the NIOSH, ACGIH, and OSHA criteria, NIOSH concluded that the effects were probably due to the additive combination of the solvents. Experimental studies in humans exposed by inhalation are discussed in Section 2.2.1 and have been summarized in several publications (Browning and Curry 1994; EPA 1984; NIOSH 1990; Tyler 1984). Experimental studies in humans and animals exposed dermally to 2-butoxyethanol or 2-butoxyethanol acetate are discussed below. No studies were located describing the effects of dermal exposure to 2-butoxyacetic acid in humans or animals.

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to 2-butoxyethanol or 2-butoxyethanol acetate.

A dermal LD₅₀ of 2,273 mg/kg has been reported for an unspecified strain and number of rats (Carpenter and Condra 1961). The compound was placed on the clipped skin of the trunk, and the skin was occluded for 4 hours. Several investigators have reported acute dermal LD₅₀ values for rabbits, which generally ranged from 406 to 1,804 mg/kg (Carpenter et al. 1956; Eastman Kodak 1988; Olin 1976; Union Carbide 1980a, 1980b). In one determination, female New Zealand rabbits appeared to be more sensitive than male New Zealand rabbits to the lethality of 2-butoxyethanol, with LD₅₀ values reported to be 568 mg/kg for females

2. HEALTH EFFECTS

and 638 mg/kg for males (Union Carbide 1980a). However, one study reported an acute dermal LD₅₀ value of 220 mg/kg for an unspecified strain and sex of rabbits, in which four of four rabbits treated with 252 mg/kg for 24 hours died within 2-7 days (Dow 1959). Another study reported an acute dermal LD₅₀ (8-hour) as low as 99 mg/kg for female New Zealand rabbits (Duprat and Gradiski 1979). In this study, groups of six female rabbits were exposed dermally (with the use of vials) to several dose levels for 8 hours and observed for 15 days. Mortality incidences were 0 of 6 in controls, 2 of 6 at 72 mg/kg, 2 of 6 at 90 mg/kg, 4 of 6 at 108 mg/kg, 5 of 6 at both 135 and 180 mg/kg, and 6 of 6 at 225 mg/kg. Deaths occurred on days 1-8 after treatment; early deaths were attributed to narcosis or failure of respiration or cardiac function, while delayed deaths were observed after weight loss and were probably due to renal impairment.

In acute dermal studies by Carpenter et al. (1956), extreme congestion of the kidney, hemoglobinuria, pale liver, and engorged spleen were noted in the rabbits that died. Deaths occurred at dose levels of 403-1,804 mg/kg for undiluted 2-butoxyethanol. In New Zealand rabbits of unspecified sex to which 250, 500, 1,000 or 2,000 mg/kg 2-butoxyethanol was applied to clipped, abraded skin and occluded for 24 hours, 1 of 4 died at 500 mg/kg on day 12, and 10 of 10 died at 1,000 and 2,000 mg/kg on days 1-2 (Olin 1976). At 24 hours, rabbits exposed to 1,000 mg/kg/day exhibited flaccid muscle tone and hematuria, whereas rabbits exposed to 2,000 mg/kg/day exhibited lacrimation, hematuria, flaccid muscle tone, and anorexia (Olin 1976). No treatment-related deaths occurred in male or female New Zealand rabbits to which doses of ≤ 361 mg/kg/day were applied to the clipped, occluded skin for 6 hours per day for nine applications over 11 days (Union Carbide 1980a).

In a developmental study, application of 2-butoxyethanol four times per day at 0.35 mL per application (1.4 mL/day) to the shaved interscapular skin of pregnant Sprague-Dawley rats on gestational days 7-16 was lethal in 10 of 11 rats on treatment days 3-7 (Hardin et al. 1984). Pregnant rats were subsequently tested at 0.12 mL per treatment (0.48 mL/day), which caused no mortality. No deaths were observed in guinea pigs in which undiluted 2-butoxyethanol (2,000 mg/kg) was placed on the dorsal skin that had been clipped free of hair (Shepard 1994a). The treated area was covered with an occlusive wrap for 24 hours. In guinea pigs exposed epicutaneously to 0.5 or 2.0 mL 2-butoxyethanol and observed for 35 days, 13 of 20 guinea pigs in the high-dose group died within the 1st week, but none died thereafter (Wahlberg and Boman 1979). No animals died in the low-dose group.

2. HEALTH EFFECTS

In an intermediate-duration study, no treatment-related deaths were found in male and female New Zealand rabbits exposed dermally to 2-butoxyethanol at 0, 10, 50, or 150 mg/kg/day, 6 hours per day, 5 days per week for 90 days (CMA 1983).

In an acute dermal LD₅₀ determination for 2-butoxyethanol acetate, doses of 3,191, 3,957, 4,766, 5,957, or 10,000 mg/kg were applied to the clipped, occluded skin of New Zealand rabbits for 24 hours (Truhaut et al. 1979). The rabbits were kept under observation for 14 days after exposure. The applied doses of 3,191, 2,957, 4,766, 5,957, and 10,000 mg/kg were reported to correspond to absorbed doses of 610, 910, 1,130, 1,830, and 2,200 mg/kg, respectively. The LD₅₀ for rabbits was reported to be approximately 1,500 mg/kg of the absorbed dose, which would correspond to an applied dose of between 4,766 and 5,957 mg/kg. The rabbits generally died between 24 and 48 hours after application and no later than 4 days after exposure.

The LD₅₀ values for rabbits and all LOAEL values from each reliable study for death in each species duration category are recorded in Tables 2-6 and 2-7.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, ocular, or body weight effects in humans. No studies were located describing respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, ocular, or body weight effects in humans or gastrointestinal, musculoskeletal, or body weight effects in animals following dermal exposure to 2-butoxyethanol acetate. Available data pertaining to systemic effects of both compounds are presented below.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Tables 2-6 and 2-7.

Respiratory Effects. Female New Zealand outbred rabbits were epicutaneously exposed to 2-butoxyethanol (Duprat and Gradiski 1979). Several doses of 72-225 mg/kg of the undiluted substance (analytical grade, purity >99.5%) were directly applied over 8 hours onto the clipped back (using vials) of the unrestrained rabbits. Animals were observed daily over a 15-day period. Macroscopic and microscopic examinations were performed on dead animals (death was observed in all dose groups) and those surviving on the 15th day. Respiratory irritation appeared as congestion and thickening of alveolar walls, similar to

Table 2-6. Levels of Significant Exposure to 2-Butoxyethanol - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
ACUTE EXPOSURE						
Death						
Rat (NS)	4 hr				2273 F (LD ₅₀) mg/kg	Carpenter and Condra 1961
Rat (Sprague- Dawley)	Gd 7-16 4x/d				1.4 mL/d F (death in 10/11)	Hardin et al. 1984
Gn Pig (NS)	once				2.0 mL (13/20 died within 1 week)	Wahlberg and Boman 1979
Rabbit (New Zealand)	24 hr				406- M (LD ₅₀) 1804 mg/kg	Carpenter et al. 1956
Rabbit (NS)	24 h				220 (LD ₅₀) mg/kg	Dow 1959
Rabbit (New Zealand)	8 hr				72 F (death in 2/6 on day 5) mg/kg 99 F (LD ₅₀) mg/kg	Duprat and Gradiski 1979
Rabbit (NS)	NS				435 (LD ₅₀) mg/kg	Eastman Kodak 1988
Rabbit (New Zealand)	24 hr				2000 (10/10 animals died) mg/kg	Olin 1976
Rabbit (New Zealand)	24 hr				580 (LD ₅₀) mg/kg	Olin 1976

Table 2-6. Levels of Significant Exposure to 2-Butoxyethanol - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference	
				Less Serious	Serious		
Rabbit (New Zealand)	once 6 hr					638 M (LD ₅₀) mg/kg 568 F (LD ₅₀) mg/kg	Union Carbide 1980a
Systemic							
Human	4-8 hr	Ocular	98 ppm	113 ppm	(ocular irritation)		Carpenter et al. 1956
Human	24-72 hr	Dermal	0.2 mL 10%				CMA 1992; Greenspan et al. 1995
Human	2 hr	Dermal		100% M	(drying of the skin, reduction in skinfold thickness and volume of exposed fingers)		Johanson et al. 1988
Rat (Wistar)	once	Hemato	200 F mg/kg			260 F (hemolysis, hemoglobinuria) mg/kg	Bartnik et al. 1987
Rat (Sprague- Dawley)	Gd 7-16 4x/d	Hemato				1.4 mL/d F (burgundy-colored urine [hemoglobinuria])	Hardin et al. 1984
		Dermal		1.4 mL/d F	(necrosis of tail; rough coat)		
Rat (Sprague- Dawley)	Gd 7-16 4x/d	Bd Wt		0.48 F mL/d	(16% decrease in body weight gain days 5-12; 13% decrease in body weight gain days 5-17)		Hardin et al. 1984

Table 2-6. Levels of Significant Exposure to 2-Butoxyethanol - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Rat (Fischer- 344)	Gd 6-15 6 hr/d	Ocular		25 ppm F	(periocular wetness)	Tyl et al. 1984
Gn Pig (NS)	once	Bd Wt	0.5 mL			Wahlberg and Boman 1979
Rabbit (New Zealand)	24 hr	Hemato			406 M (hemoglobinuria) mg/kg	Carpenter et al. 1956
		Hepatic			406 M (pale liver) mg/kg	
		Renal			406 M (congested kidneys) mg/kg	
Rabbit (New Zealand)	3 min	Hemato		505 M (increased erythrocyte osmotic fragility) mg/kg		Carpenter et al. 1956
Rabbit (NS)	24 h	Dermal		200 (moderate skin irritation) mg/kg		Dow 1959
		Ocular			100% (moderate conjunctival irritation; corneal injury)	
		Bd Wt		200 (slight initial weight loss) mg/kg		

Table 2-6. Levels of Significant Exposure to 2-Butoxyethanol - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference		
				Less Serious	Serious			
Rabbit (New Zealand)	8 hr	Resp		72 F mg/kg	(congestion, thickening of alveolar walls)	Duprat and Gradiski 1979		
		Hemato			72 mg/kg F (hemoglobinuria)			
		Hepatic			72 mg/kg F (congestion in liver, necrosis and steatosis)			
		Renal			72 mg/kg F (enlarged kidneys with hemoglobinuric nephrosis and interstitial reaction)			
		Dermal		72 F mg/kg	(necrosis of epidermis and dermis)			
		Other			72 mg/kg F (hypothermia)			
Rabbit (New Zealand)	once	Ocular		0.1 mL of 10%	(mild eye irritation)	0.1 mL of 100%	(severe eye irritation)	Kennah et al. 1989a
Rabbit (New Zealand)	24 hr	Gastro	500 mg/kg			1000 mg/kg	(very dark areas in small intestine)	Olin 1976
		Musc/ske	500 mg/kg			1000 mg/kg	(flaccid muscle tone)	
		Hepatic				250 mg/kg	(discolored liver)	
		Renal	250 mg/kg			500 mg/kg	(blood in urine and bladder [hematuria], discolored kidney)	
		Ocular	250 mg/kg			500 mg/kg	(yellow cornea)	
Rabbit (New Zealand)	once or 4 hr	Dermal		0.5 mL	(moderate skin irritation)			Rohm and Haas 1983
		Ocular				0.1 mL	(severe eye irritation)	

Table 2-6. Levels of Significant Exposure to 2-Butoxyethanol - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference	
				Less Serious	Serious		
Rabbit (New Zealand)	Gd 6-18 6 hr/d	Ocular	50 ppm F	100 ppm F (periocular wetness)		Tyl et al. 1984	
Rabbit (New Zealand)	11 d 9 x 1 mL/d 6 hr/d	Hemato	180 M mg/kg/d	361 M (transient hemoglobinuria) mg/kg/d		Union Carbide 1980a	
			180 F mg/kg/d	361 F (reduced mean erythrocyte counts, hemoglobin, MCHC; increased MCH)			
		Hepatic	361 mg/kg/d				
		Renal	90 F mg/kg/d	180 F (blood in urine [hematuria]) mg/kg/d			
		Dermal		18 mg/kg/d	(erythema)		
		Ocular	361 M mg/kg/d				
Bd Wt	361 M mg/kg/d						
	180 F mg/kg/d	361 F (121% decrease in weight gain on day 3)					

Table 2-6. Levels of Significant Exposure to 2-Butoxyethanol - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference	
				Less Serious	Serious		
Rabbit (New Zealand)	once 6 hr	Gastro	451 mg/kg	902 mg/kg	(reddened stomach; females: reddened intestines)	Union Carbide 1980a	
		Hemato					451 F (hemoglobinuria) mg/kg
		Hepatic	451 mg/kg	902 mg/kg	(mottled with pocked surface)		
		Renal					451 (hematuria; enlarged, dark mg/kg kidneys; male survivors had pocked surface)
		Endocr		451 mg/kg	(reddened adrenals)		
		Dermal		451 mg/kg	(erythema; females: slight necrosis at application site)		
		Ocular	451 M mg/kg 902 F mg/kg				902 M (grey iris) mg/kg
		Other	451 mg/kg	902 mg/kg	(yellowed peritoneal fat)		
Rabbit (New Zealand)	11 d 9 x 1 mL/d 6 hr/d	Renal		271 mg/kg/d	(tubular vacuolization [4/6] degeneration [6/6] hyperplasia [3/6], glomerular adhesions [4/6], interstitial nephritis [3/6], hemoglobinuric nephrosis)	Union Carbide 1980a	
		Dermal		271 mg/kg/d	(necrosis)		

Table 2-6. Levels of Significant Exposure to 2-Butoxyethanol - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Rabbit (New Zealand)	24 hr	Resp			451 M (orange-red lungs)	Union Carbide 1980b
		Gastro			451 M (orange peritonea, intestines)	
		Hepatic			451 M (orange-red liver)	
		Renal			451 M (dark red kidneys, hematuria)	
		Dermal	451 M mg/kg	902 M (erythema, necrosis)		
		Ocular	451 M mg/kg		902 M (iritis in 2/4)	
Rabbit (NS)	once	Ocular	0.5 mL 5%	0.5 mL 15%	(moderate corneal injury)	Union Carbide 1980b
Rabbit (New Zealand)	4 hr	Dermal		0.5 mL	(irritant)	Zissu 1995
Rabbit (New Zealand)	24 hr	Dermal			0.5 mL (severe irritant)	Zissu 1995
Immunological/Lymphoreticular						
Human	24-72 hr		0.2 mL 10%			CMA 1992; Greenspan et al. 1995
Rabbit (New Zealand)	24 hr				406 M (engorged spleen)	Carpenter et al. 1956

Table 2-6. Levels of Significant Exposure to 2-Butoxyethanol - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Rabbit (New Zealand)	8 hr				72 mg/kg F (enlarged spleens filled with erythrocytes, white atrophic pulp)	Duprat and Gradiski 1979
Rabbit (New Zealand)	once 6 hr		902 M mg/kg			Union Carbide 1980a
			451 F mg/kg	902 F (enlarged spleen) mg/kg		
Rabbit (New Zealand)	once				451 M (dark spleens) mg/kg	Union Carbide 1980b
Neurological						
Rat (Sprague-Dawley)	Gd 7-16 4x/d				1.4 mL/d F (ataxia; moderate to marked inactivity)	Hardin et al. 1984
Rabbit (New Zealand)	8 hr				72 mg/kg F (prostration, narcosis prior to death)	Duprat and Gradiski 1979
Rabbit (New Zealand)	24 hr		1000 mg/kg		2000 mg/kg (anorexia, no spontaneous movement)	Olin 1976
Rabbit (New Zealand)	once 6 hr		902 M mg/kg			Union Carbide 1980a
			451 F mg/kg		902 F (nystagmus, convulsions) mg/kg	

Table 2-6. Levels of Significant Exposure to 2-Butoxyethanol - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Developmental						
Rat (Sprague- Dawley)	Gd 7-16 4x/d		0.48 mL/d			Hardin et al. 1984
INTERMEDIATE EXPOSURE						
Systemic						
Rabbit (New Zealand)	90 d 5 d/wk 6 hr/d	Resp	150 mg/kg			CMA 1983
		Cardio	150 mg/kg			
		Gastro	150 mg/kg			
		Hemato	150 mg/kg			
		Musc/ske	150 mg/kg			
		Hepatic	150 mg/kg			
		Renal	150 mg/kg			
		Endocr	150 mg/kg			
		Dermal		10 mg/kg	(slight to moderate erythema and edema)	
		Ocular	150 mg/kg			
		Bd Wt	150 mg/kg			

Table 2-6. Levels of Significant Exposure to 2-Butoxyethanol - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Immunological/Lymphoreticular						
Rabbit (New Zealand)	90 d 5 d/wk 6 hr/d		150 mg/kg			CMA 1983
Neurological						
Rabbit (New Zealand)	90 d 5 d/wk 6 hr/d		150 mg/kg			CMA 1983
Reproductive						
Rabbit (New Zealand)	90 d 5 d/wk 6 hr/d		50 mg/kg M 150 F mg/kg	150 M (5.2% increase in relative mg/kg testes weight)		CMA 1983

Bd Wt = body weight; d = day(s); Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestation day; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); LD₅₀ = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; min = minute(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = times

Table 2-7. Levels of Significant Exposure to 2-Butoxyethanol Acetate - Oral

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
				Less Serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE						
Death						
Rat (Wistar)	once (GO)				3000 M (LD ₅₀) 2400 F (LD ₅₀)	Truhaut et al. 1979

Cardio = cardiovascular; Endocr = endocrine; HGB = hemoglobin; Hemato = hematological; hr = hour(s); LD₅₀ = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-adverse-effect level; RBC = red blood cells; Resp = respiratory

2. HEALTH EFFECTS

interstitial pneumonitis. In another study, male New Zealand white rabbits given a single dose of 0.5 mL/kg 2-butoxyethanol that remained in contact with intact skin for 24 hours showed orange-red lungs at necropsy (Union Carbide 1980b). Death of one of four animals occurred at this dose. Neither clinical signs of respiratory effects nor gross pathology changes in the trachea and lungs were observed in guinea pigs treated with a single dermal dose of 2,000 mg/kg/day 2-butoxyethanol (Shepard 1994a). The treated area was occluded for 24 hours. Histological examination of the lungs revealed no adverse treatment-related lesions of male and female New Zealand rabbits dosed with ≤ 150 mg/kg/day 2-butoxyethanol 16 hours per day, 5 days per week, for 90 days (CMA 1983).

New Zealand rabbits given 24-hour applications of 2-butoxyethanol acetate to the clipped, occluded skin at doses of 3,191-10,000 mg/kg as part of a lethality study exhibited no adverse respiratory clinical signs or histopathological changes in the lungs (Truhaut et al. 1979).

Cardiovascular Effects. Gross changes in the heart at necropsy were not observed in guinea pigs treated with a single dermal dose of 2,000 mg/kg/day 2-butoxyethanol (Shepard 1994a). The treated area was occluded for 24 hours. No effects on heart weight and no histopathological lesions in the aorta or heart were observed in male or female New Zealand rabbits dosed with ≤ 150 mg/kg/day 2-butoxyethanol 16 hours per day, 5 days per week, for 90 days (CMA 1983).

New Zealand rabbits given 24-hour applications of 2-butoxyethanol acetate to the clipped, occluded skin at doses of 3,191-10,000 mg/kg as part of a lethality study exhibited no histopathological changes in the heart (Truhaut et al. 1979).

Gastrointestinal Effects. Male and female New Zealand white rabbits were dosed dermally once with 451 or 902 mg/kg 2-butoxyethanol, and occluded exposure was maintained for 6 hours (Union Carbide 1980a). All rabbits in the 902-mg/kg dose group died and exhibited reddened stomachs at necropsy; females also had reddened intestines. Rabbits in the 451-mg/kg dose group had no remarkable gastrointestinal findings, and all except one female survived the experiment. However, in a companion study of male New Zealand rabbits that were similarly exposed dermally for a 24-hour period to 451 or 902 mg/kg, gross necropsy of the rabbits that died at 451 mg/kg (one of four) and 902 mg/kg (four of four) revealed orange peritonea and intestines (Union Carbide 1980b). Very dark intestines were also observed in one rabbit dosed with 1,000 mg/kg 2-butoxyethanol on abraded skin (Olin 1976). All four animals treated at this dose died. Gross examination of the esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, and rectum did not

2. HEALTH EFFECTS

reveal any adverse effects in guinea pigs treated with a single dermal dose of 2,000 mg/kg/day 2-butoxyethanol (Shepard 1994a). The treated area was occluded for 24 hours. Histological examination of the stomach (pylorus and fundus) and of the intestines (cecum, duodenum, jejunum, ileum, colon) revealed no pathological lesions in male and female New Zealand rabbits dosed with 10, 50, or 150 mg/kg/day 2-butoxyethanol 6 hours per day, 5 days per week, for 90 days (CMA 1983). One male in the 50-mg/kg/day dose group that was found dead on day 15 of the study had a gastric ulcer. Neither the ulcer nor the death appeared to be related to treatment.

Hematological Effects. Dermal exposure of animals to 2-butoxyethanol has also resulted in hemolysis of red blood cells and hemoglobinuria. Doses ranging from 200 to 500 mg/kg 2-butoxyethanol were applied to the shaved dorsal skin of female Wistar rats; hemolysis was observed in two of three animals at 260 mg/kg, and hemoglobinuria was observed in one of three animals (Bartnik et al. 1987). A dose of 500 mg/kg caused increased mean corpuscular volume, decreased erythrocyte count and hemoglobin level, and hemoglobinuria within 6 hours after exposure. In another study, 61, 181, or 299 mg/kg [¹⁴C]2-butoxy- ethanol was applied to the clipped backs of male Fischer 344 rats, and nonoccluded percutaneous absorption was measured (Sabourin et al. 1992b, 1993). In the 181-mg/kg dose group, no significant hemolysis was detected; hematology was not evaluated at the other doses. Water or undiluted 2-butoxyethanol (0.35 mL) was applied four times daily (1.4 mL/day) on gestational days 7-16 to the shaved interscapular skin of pregnant Sprague-Dawley rats (Hardin et al. 1984). Burgundy-colored urine, presumably from hemoglobin in the urine, was observed by the end of the 1st day of treatment with 2-butoxyethanol. Ten of 11 treated rats died during gestation days 9-13.

Male albino New Zealand rabbits exhibited increased erythrocyte osmotic fragility 1 hour after a 3-minute skin contact period with 505 mg/kg 2-butoxyethanol (Carpenter et al. 1956). Hemoglobinuria was also observed in New Zealand rabbits that died after 24-hour skin contact with ≥ 406 mg/kg (Carpenter et al. 1956). In male and female New Zealand rabbits to which 451 or 902 mg/kg 2-butoxyethanol was applied to the skin (occluded) for 6 hours, hemoglobinuria was observed in both dose groups (Union Carbide 1980a). Lethality was one of eight at 451 mg/kg and all 8 rabbits at 902 mg/kg. Similarly, hemoglobinuria was noted prior to death in female New Zealand white rabbits treated dermally with ≥ 72 mg/kg 2-butoxyethanol over an 8-hour period (Duprat and Gradiski 1979). Clipped male and female New Zealand white rabbits received daily dermal (occluded) applications of 1 mL/day of 0%, 5%, 25%, 50%, or 100% concentrations (0, 18, 90, 180, or 361 mg/kg/day, respectively) of 2-butoxyethanol for a total of nine applications over an 11-day period (Union Carbide 1980a). The rabbits were subjected to covered dermal exposure for 6 hours per day.

2. HEALTH EFFECTS

Transient hemoglobinuria was observed at the high dose in males. In addition, females exhibited increases in mean corpuscular hemoglobin (MCH) and decreases in red blood cell count, hemoglobin, and mean corpuscular hemoglobin concentrations (MCHC) at 361 mg/kg/day.

No adverse treatment-related hematological effects (on white blood cells, red blood cells, hemoglobin, hematocrit, and mean corpuscular volume) were noted in male or female New Zealand rabbits dosed with ≤ 150 mg/kg/day 2-butoxyethanol 16 hours per day, 5 days per week, for 90 days (CMA 1983).

New Zealand rabbits were given 24-hour applications of 2-butoxyethanol acetate to the clipped, occluded skin at doses of 3,191-10,000 mg/kg as part of a lethality study (Truhaut et al. 1979). In treated rabbits, a decrease in hemoglobin, a 20-25% decrease in red blood cell count, and marked hemoglobinuria and/or hematuria were observed; for each dose group, some rabbits had almost normal values while others were severely affected.

The hemolytic effect of 2-butoxyethanol and 2-butoxyethanol acetate has been associated in animal studies with changes in the spleen, including engorgement and erythrocytic infiltration. These effects are discussed further in Section 2.2.3.3, Immunological and Lymphoreticular Effects.

Musculoskeletal Effects. Flaccid muscle tone, probably neurological in origin, was observed prior to death in rabbits dosed with 1,000 or 2,000 mg/kg 2-butoxyethanol on abraded, occluded skin for 24 hours (Olin 1976). Histological examination of skeletal muscle and bone (sternum) revealed no lesions in male or female New Zealand rabbits dosed with up to 150 mg/kg/day 2-butoxyethanol 16 hours per day, 5 days per week, for 90 days (CMA 1983).

Hepatic Effects. Pale livers were observed in New Zealand rabbits that died after 24-hour skin contact with ≥ 406 mg/kg (Carpenter et al. 1956). Female New Zealand outbred rabbits were epicutaneously exposed to ≥ 72 mg/kg 2-butoxyethanol (Duprat and Gradiski 1979). Histopathological examinations of animals that died prior to the end of the 15-day observation period showed congestion in the liver, with small necrotic foci with mesenchymatous reactions and inconstant (i.e., not always present) steatosis. A single 6-hour occluded dermal exposure of male and female New Zealand white rabbits to 451 and 902 mg/kg 2-butoxyethanol caused mottled livers with pocked surfaces in animals that died (Union Carbide 1980a). In a companion study, in which male rabbits were exposed to the same doses for 24 hours, discolored livers were observed at both doses (Union Carbide 1980b). Discolored or pale liver has also been observed in New Zealand rabbits

2. HEALTH EFFECTS

dosed with 250-1,000 mg/kg 2-butoxyethanol on abraded skin (Olin 1976). Gross examination of the liver did not reveal any adverse effects in guinea pigs treated with a single dermal dose of 2,000 mg/kg/day 2-butoxyethanol (Shepard 1994a); the treated area was occluded for 24 hours. No effect on liver weight was seen in male or female New Zealand white rabbits exposed dermally to 0, 18, 90, 180, or 361 mg/kg/day of 2-butoxyethanol for a total of nine applications over an 11-day period with a duration of 6 hours of exposure per day (Union Carbide 1980a). Histological examination of livers and gall bladders revealed no lesions in male or female New Zealand rabbits dosed with up to 150 mg/kg/day 2-butoxyethanol 6 hours per day, 5 days per week, for 90 days (CMA 1983). In addition, no effects on liver weight were observed.

New Zealand rabbits given 24-hour applications of 2-butoxyethanol acetate to the clipped, occluded skin at doses of 3,191-10,000 mg/kg as part of a lethality study exhibited no histopathological changes in the liver (Truhaut et al. 1979).

Renal Effects. Congested kidneys were observed in New Zealand rabbits that died after 24-hour skin contact with ≥ 406 mg/kg (Carpenter et al. 1956). Female New Zealand outbred rabbits epicutaneously exposed to 2-butoxyethanol at doses of 0, 72, 90, 1108, 135, 180, and 225 mg/kg of the undiluted substance (directly applied over 8 hours onto the clipped back of the unrestrained rabbits) showed adverse kidney effects (Duprat and Gradski 1979). Enlarged kidneys with extensive hemoglobinuric nephrosis and interstitial reaction were observed in rabbits in each dose group (≥ 72 mg/kg) that died. Rabbits that survived and were sacrificed for macroscopic and microscopic examinations showed no differences from control animals at 72 and 90 mg/kg of exposure. Some rabbits in the groups receiving 108, 135, 180, and 225 mg/kg showed persistent kidney lesions (not specified), but the other previously stated morphological changes were not observed. The study authors concluded that the morphological changes in the kidneys suggested damage due to *in vivo* hemolysis. A single 6-hour occluded dermal exposure of male and female New Zealand white rabbits to 451 or 902 mg/kg 2-butoxyethanol caused hematuria at both doses with enlarged, dark kidneys in animals in the high-dose group and kidneys with pocked surfaces in the males of the 451 -mg/kg/day dose group (Union Carbide 1980a). One of eight rabbits died at 451 mg/kg and all eight rabbits died at 902 mg/kg. In a companion study in which male rabbits were exposed to the same doses for 24 hours, dark red kidneys and bloody urine were observed at both doses (Union Carbide 1980b). Discolored kidneys and bloody urine (hematuria) have also been observed in New Zealand rabbits dosed with 500-2,000 mg/kg 2-butoxyethanol on abraded, occluded skin (Olin 1976). Gross examination of the kidneys did not reveal any adverse effects in guinea pigs treated with a single dermal dose of 2,000 mg/kg/day 2 butoxyethanol; the treated area was occluded for 24 hours (Shepard 1994a).

2. HEALTH EFFECTS

Increased urinary protein was seen in male and female New Zealand white rabbits exposed dermally for 6 hours per day to 361 mg/kg/day of 2-butoxyethanol for a total of nine applications over an 11-day period; however, rabbits exposed to 271 mg/kg/day 2-butoxyethanol nine times over 11 days had renal effects including dimpling of the renal surface, tubular vacuolization, tubular degeneration, tubular cell hyperplasia, glomerular adhesions, and interstitial nephritis (Union Carbide 1980a). Hematuria was observed in female rabbits exposed to 180 or 361 mg/kg/day 2-butoxyethanol (Union Carbide 1980a). No effects on kidney weight and no treatment-related histopathological lesions in the kidney or urinary bladder were noted in male and female New Zealand rabbits dosed with ≤ 150 mg/kg/day 2-butoxyethanol 16 hours per day, 5 days per week, for 90 days (CMA 1983).

New Zealand rabbits exposed dermally to doses of 3,191-10,000 mg/kg 2-butoxyethanol acetate for 24 hours exhibited renal effects (Truhaut et al. 1979). Necropsy revealed bloody kidneys and the presence of large quantities of blood in the bladder (hematuria). The severity of the histopathological renal lesions (necrotizing, hemorrhagic, and atrophic acute tubular nephrosis with occasional glomerular lesions) was reported to be dose-related, but the specific doses at which they occurred were not reported. Histopathologic examination of a section from the kidney of a rabbit treated with 10,000 mg/kg 2-butoxyethanol acetate showed atrophic tubular dilation, tubular fatty degeneration, vacuolar degeneration, and hemosiderin deposits in the glomerulus and the tubular cells, with glomerular retraction and luminal hyaline deposits, luminal granular deposits, foci of cellular lysis, occasional interstitial fibro-inflammatory organization, and parietal atrophy. Presumably, some of these lesions were also observed in rabbits that died. When the surviving animals were sacrificed after the 2-week observation period, no gross pathologic or histopathological lesions in the kidney were noted.

Endocrine Effects. A single 6-hour occluded dermal exposure of male and female New Zealand white rabbits to 451 or 902 mg/kg 2-butoxyethanol caused reddened adrenal glands in both dose groups (Union Carbide 1980a). One of eight rabbits died at 451 mg/kg and all eight rabbits died at 902 mg/kg. Gross examination of the pituitary and adrenal glands did not reveal any adverse effects in guinea pigs treated with a single dermal dose of 2,000 mg/kg/day 2-butoxyethanol (Shepard 1994a); the treated area was occluded for 24 hours. Histological examination of adrenals, pancreas, pituitary, thyroid, and parathyroid glands revealed no pathological lesions in male or female New Zealand rabbits dosed with ≤ 150 mg/kg/day 2-butoxyethanol 6 hours per day, 5 days per week, for 90 days (CMA 1983).

2. HEALTH EFFECTS

New Zealand rabbits given 24-hour dermal exposure to 2-butoxyethanol acetate at doses of 3,191-10,000 mg/kg as part of a lethality study exhibited no histopathological changes in the pancreas or adrenal gland (Truhaut et al. 1979).

Dermal Effects. Percutaneous absorption of 2-butoxyethanol was investigated in 12 exposure experiments with five men (Johanson et al. 1988). None had been previously exposed occupationally to industrial solvents. All had participated in a previous inhalation study of 2-butoxyethanol (Johanson et al. 1986a). The subjects kept two or four fingers immersed in neat 2-butoxyethanol for 2 hours. None of the subjects exhibited adverse reaction from the exposure to 2-butoxyethanol. Although the skin of the exposed fingers was not irritated, it was wrinkled and seemed to be more rigid and less elastic after exposure. This effect reached a maximum at 2-4 hours after the end of the exposure. The volume and skinfold thickness of the exposed fingers decreased, then returned to normal. A drying pattern with small fissures appeared on the skin, which disappeared after 1-2 days.

Volunteers (214 men and women) were given 0.2 mL 10% 2-butoxyethanol in patches applied to the intrascapular area of the back, either to the right or left of the midline (CMA 1992; Greenspan et al. 1995). A 10% concentration was used because it is the highest concentration of 2-butoxyethanol found in cosmetic products, although concentrations as high as 50% can be found in cleaning products which should be diluted before use (OECD 1997). The entire study extended over a 6-week period and involved three phases: induction, rest, and challenge. The induction phase consisted of nine consecutive applications of 2-butoxyethanol and was assessed after 24-72 hours of patch application. The subjects were required to remove the patches approximately 24-72 hours after application; they were evaluated and identical patches reapplied. Following the ninth evaluation, the subjects were dismissed for a 14-day rest period. The challenge phase of the experiment was initiated during the 6th week of the study, with identical patches applied to sites previously unexposed to 2-butoxyethanol. These patches were removed by subjects after 24 hours, and the sites were graded 48 and 72 hours after application. Subjects who had six applications or more, with subsequent readings during induction, and at least one reading during challenge, were considered a completed case. One individual had erythema on the second challenge, 7 had barely perceptible erythema on the first challenge, and 12 had barely perceptible erythema on the second challenge. The study authors concluded that there were no dermal effects of 10% 2-butoxyethanol under the conditions applied in this study; 201 subjects completed the study.

2. HEALTH EFFECTS

Water or undiluted 2-butoxyethanol was applied four times daily (0.35 mL per application or 1.4 mL/day) on gestational days 7-16 to the shaved interscapular skin of pregnant Sprague-Dawley rats with an automatic pipetter. Progressive necrosis of the tail (which may have been associated with the toxic effects of 2-butoxyethanol on red blood cells and subsequent vascular response) and rough coats were noted in some treated rats (Hardin et al. 1984). Severe skin irritation has been noted in guinea pigs after application of 2-butoxyethanol (dose not specified) (Eastman Kodak 1988). In another study, female New Zealand rabbits exposed to ≥ 72 mg/kg for 8 hours developed cutaneous lesions accompanied by necrosis of epidermis and dermis on the 4th day after exposure (Duprat and Gradiski 1979). Skin lesions healed within a 2-week period. In other studies, application of 0.5 mL undiluted compound (Rohm and Haas 1983), unspecified amounts of undiluted compound (Dow 1958, 1981; Eastman Kodak 1988), or doses of 200 or 252 mg/kg 2-butoxyethanol (Dow 1959) to rabbit skin resulted in hyperemia, edema, slight exfoliation, and/or slight-to-moderate irritation. A single 6-hour occluded dermal application of 451 or 902 mg/kg 2-butoxyethanol to male and female New Zealand white rabbits caused slight necrosis in females at both doses and erythema in both sexes at both doses (Union Carbide 1980a). However, in a companion study in which male rabbits were exposed to the same doses for 24 hours, erythema and necrosis were noted at the high dose only (Union Carbide 1980b). Erythema was also seen in male and female New Zealand white rabbits exposed dermally to 18-361 mg/kg/day of 2-butoxyethanol for a total of nine applications over an 11 -day period with an exposure duration of 6 hours per day; male and female rabbits exposed to 271 mg/kg/day for nine times over 11 days also showed dermal necrosis (Union Carbide 1980a). A single dose of 0.01 mL of undiluted 2-butoxyethanol applied to the clipped bellies of New Zealand white rabbits caused moderate capillary congestion in two of five rabbits (grade 2) (Union Carbide 1980b). Dermal irritation from 2-butoxyethanol exposure has been studied in New Zealand rabbits using both the Draize protocol (24-hour occluded exposure) and the European Economic Communities protocol (4-hour occluded exposure) (Zissu 1995). For both protocols, 0.5 mL of undiluted 2-butoxyethanol was placed on the skin. 2-Butoxyethanol was considered a severe irritant by the Draize protocol and an irritant by the European Economic Communities protocol. Slight-to-moderate erythema was noted in male and female New Zealand rabbits dosed with 10-150 mg/kg/day 2-butoxyethanol 6 hours per day, 5 days per week, for 90 days (CMA 1983). Slight-to-moderate scaling and flaking were occasionally noted during weeks 2 and 3 and recurred sporadically through 91 days.

2-Butoxyethanol acetate was used to evaluate a noninvasive human method and an *in vitro* cytotoxicity method as alternatives to the rabbit skin test for primary irritant effects (Jacobs et al. 1989). The human method included measurements of cutaneous blood flow values (CBFV) by laser Doppler flowmetry before and after patch application on the forearm; some experiments used 100% test substances (75 mg/cm²)

2. HEALTH EFFECTS

applied for 48 hours and measured 12 hours later, and other experiments used 10% solutions of test substances (7.5 mg/ m^3) applied for 3 hours and measured 1, 24, 48, and 72 hours later. Cutaneous blood flow values (CBFV) obtained in the two series of experiments (10% for 3 hours and 100% for 48 hours) resulted in a ranking of 2, which is the minimal mean erythema needed to classify substances as skin irritants. The CBFV in humans correlated very well ($r=0.99$) with erythema scores obtained on rabbits.

In New Zealand white rabbits, patches soaked with 0.5 mL of undiluted 2-butoxyethanol acetate were applied to one site of the prepared skin surface (Jacobs et al. 1989). The untreated skin was used as a control. Erythema scores were obtained 1, 24, 48, and 72 hours after application of the undiluted substance for 4 hours. The erythema scores of exposure to 100% 2-butoxyethanol acetate for 4 hours in rabbits showed a ranking of 2, which is the minimal mean erythema needed to classify substances as skin irritants. New Zealand rabbits exposed dermally to unspecified doses of 2-butoxyethanol acetate for 24 hours exhibited dermal effects (Truhaut et al. 1979). When 2-butoxyethanol acetate was tested for primary irritation of the skin, four of six rabbits showed slight erythema (grade 1) at 24 hours. Dermal irritation from exposure to 2-butoxyethanol acetate has been studied in rabbits using both the Draize protocol (24-hour occluded exposure) and the European Economic Communities protocol (4-hour occluded exposure) (Zissu 1995). For both protocols, 0.5 mL of undiluted 2-butoxyethanol acetate was placed on the skin. 2-Butoxyethanol acetate was considered a moderate irritant by the Draize protocol and non-irritating by the European Economic Communities protocol.

Ocular Effects. Male and female volunteers exposed by inhalation to 98, 113, or 195 ppm 2-butoxyethanol for 4-8 hours experienced ocular irritation during exposure to 113 and 195 ppm (Carpenter et al. 1956). As discussed in Section 2.2.1.2, the ocular irritation was probably due to direct contact of the eyes with the 2-butoxyethanol vapor.

Pregnant Fischer 344 rats dosed by inhalation during gestational days 6-15 with 25-200 ppm 2-butoxyethanol exhibited periocular wetness at all concentrations. New Zealand white rabbits exposed to 100 and 200 ppm (but not to 25 ppm) during gestation exhibited the same effect (Tyl et al. 1984). As noted in Section 2.2.1.2, the periocular wetness was probably due to direct contact of the eyes with the 2-butoxyethanol vapor.

The eyes of rabbits instilled with unspecified amounts of undiluted 2-butoxyethanol (Dow 1958, 1959, 1981) or 0.1 mL of undiluted 2-butoxyethanol (Rohm and Haas 1983; Union Carbide 1980b) exhibited severe eye

2. HEALTH EFFECTS

irritation, moderate-to-extensive conjunctivitis, moderate corneal damage, and/or slight iritis (Dow 1958, 1959, 1981; Rohm and Haas 1983; Union Carbide 1980b). Moderate corneal injury was observed in rabbits in which 0.5 mL of a 15% dilution of 2-butoxyethanol was placed in the conjunctival sac (Union Carbide 1980b). No effects were observed with a dilution of 5%. A single 6-hour occluded dermal exposure of male and female New Zealand white rabbits to 451 or 902 mg/kg 2-butoxyethanol caused grey iris in males in the high-dose group (Union Carbide 1980a). No ocular effects were seen at the lower dose. In a companion study in which male rabbits were given the same dermal doses for 24 hours, iritis was observed at the high dose (Union Carbide 1980b). Lacrimation was also observed prior to death in New Zealand rabbits dosed with 2,000 mg/kg 2-butoxyethanol on abraded skin, and yellow cornea was observed in animals dosed with 500 mg/kg 2-butoxyethanol (Olin 1976). No ocular effects were seen upon ophthalmological examination of male and female New Zealand white rabbits exposed dermally to 0, 18, 90, 180, or 361 mg/kg/day of 2-butoxyethanol for a total of nine applications over an 11 -day period with an exposure duration of 6 hours per day (Union Carbide 1980a).

The relationship between changes in corneal thickness (swelling) and Draize eye irritancy scores was examined to see if the former test could give equivalent results and a reduction in the variability inherent in the Draize procedure (Kennah et al. 1989a). The eyes of New Zealand albino rabbits were instilled with 0.1 mL 2-butoxyethanol at concentrations of 10%, 20%, 30%, 70%, or 100% (dilutions were prepared in polyethylene glycol as weight/weight percentage solutions) in the conjunctival sac of one defect-free eye. The other eye served as a control. The cornea, iris, and conjunctiva were scored at 24, 48, and 72 hours and at 7, 10, 14, and 21 days postdosing if irritation persisted. Corneal thickness was measured several hours before instillation of test material and thereafter at intervals coincident with the Draize scoring. A correlation with the Draize scoring procedure and corneal swelling was established. Eye irritation determination using this system showed that at 100% concentration, 2-butoxyethanol resulted in a Draize score of 66% with 19% coefficient of variation (CV), 181% corneal swelling with 9.9% CV, and was classified as severe. At 30% and 70% concentrations of 2-butoxyethanol, Draize scores were 39% and 49% with CV values of 13% and 44%; corneal swelling values were 146% and 181%, with CV values of 9.7% and 18%. The Draize scores indicated moderate irritation. At 10% and 20% concentrations of 2-butoxyethanol, Draize scores were 1% and 2%, with CV values of 100% and 70%; corneal swelling values were 91% and 113%, with CV values of 7.4% and 13%. The Draize scores indicated mild irritation.

2. HEALTH EFFECTS

Histological examination of the eyes revealed no adverse treatment-related ocular effects in male or female New Zealand rabbits dosed dermally with up to 150 mg/kg/day 2-butoxyethanol 16 hours per day, 5 days per week, for 90 days (CMA 1983).

The eyes of New Zealand rabbits instilled with an unspecified amount of 2-butoxyethanol acetate for 24 hours exhibited little effect (Truhaut et al. 1979). The eyes showed very little sign of irritancy, with only two of six rabbits showing slight conjunctival redness and discharge.

Body Weight Effects. 2-Butoxyethanol caused a 13-16% decrease in body weight gain during treatment in pregnant Sprague-Dawley rats to which undiluted 2-butoxyethanol was applied four times daily (0.12 mL, per application or 0.48 mL/day) to the shaved interscapular skin on gestational days 7-16 (Hardin et al. 1984). In guinea pigs (sex and strain not specified) exposed epicutaneously to 0.5 or 2.0 mL 2-butoxyethanol, and observed for 35 days, no effect on body weight was observed at the low dose (Wahlberg and Boman 1979). Mortality at the high dose was significant (65% within 1 week), and so no body weight measurements were made. No effects on body weight gain were observed in guinea pigs given a single dermal dose of 2,000 mg/kg and observed for 14 days (Shepard 1994a). The treated area was occluded for 24 hours. A slight but unspecified initial weight loss occurred in rabbits to which 200 mg/kg 2-butoxyethanol was applied to the skin for 24 hours (Dow 1959). No effect on body weight was seen in male New Zealand white rabbits exposed dermally to 0, 18, 90, 180, or 361 mg/kg/day of 2-butoxyethanol for a total of nine applications over an 11-day period with an exposure duration of 6 hours per day, but female rabbits exhibited a decrease in weight gain of 121% on day 3 at 361 mg/kg/day compared to control animals, and continued to lose weight until sacrificed on day 35 (Union Carbide 1980a). No adverse treatment-related effects on body weight were noted in male and female New Zealand rabbits that received dermal doses \leq 150 mg/kg/day 2-butoxyethanol 16 hours per day, 5 days per week, for 90 days (CMA 1983).

Other Effects. Pregnant Sprague-Dawley rats treated dermally four times daily with 2-butoxyethanol (0.35 mL per application or 1.4 mL/day) during gestation exhibited dark stains around the muzzle and anogenital area (Hardin et al. 1984). This may have resulted from grooming activities in the presence of hemoglobinuria. Female New Zealand white rabbits that died after dermal application of 2-butoxyethanol at \geq 72 mg/kg exhibited hypothermia (Duprat and Gradiski 1979). Yellowed peritoneal fat was observed in male and female New Zealand white rabbits that died after a single 6-hour occluded dermal exposure to 902 mg/kg 2-butoxyethanol (Union Carbide 1980a). This effect was not noted in animals exposed to 451 mg/kg, a dose that resulted in the death of one of four females and no males.

2. HEALTH EFFECTS

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after dermal exposure to 2-butoxyethanol acetate or regarding lymphoreticular effects in humans after dermal exposure to 2-butoxyethanol. No studies were located regarding immunological effects in animals after dermal exposure to 2-butoxyethanol or 2-butoxyethanol acetate.

Volunteers (214 men and women) were given 0.2 mL 10% 2-butoxyethanol in patches applied to the intrascapular area of the back, either to the right or left of the midline (CMA 1992; Greenspan et al. 1995). A 10% concentration was used because it is the highest concentration of 2-butoxyethanol found in cosmetic products. The entire study extended over a 6-week period and involved three phases: induction, rest, and challenge. The induction phase consisted of nine consecutive applications of 2-butoxyethanol, and the subjects were assessed after 24-72 hours of patch application. The subjects were required to remove the patches approximately 24-72 hours after application; they were evaluated and identical patches reapplied. Following the ninth evaluation, the subjects were dismissed for a 14-day rest period. The challenge phase of the experiment was initiated during the 6th week of the study, with identical patches applied to sites previously unexposed to 2-butoxyethanol. These patches were removed by subjects after 24 hours, and the sites were graded 48 and 72 hours after application. Subjects who had six applications or more, with subsequent readings during induction, and at least one reading during challenge, were considered completed cases. One individual had erythema on the second challenge, 7 had barely perceptible erythema on the first challenge, and 12 had barely perceptible erythema on the second challenge. The study authors concluded that there was no evidence of sensitization to 10% 2-butoxyethanol in human subjects under the conditions applied in this study; 201 subjects completed the study. However, only a 10% dilution of 2-butoxyethanol was used; concentrations as high as 50% can be found in cleaning products which should be diluted before use (OECD 1997).

2-Butoxyethanol has also been tested for dermal sensitization in guinea pigs using the maximized Magnusson and Kliman test (Zissu 1995). The sensitization test was completed over a 4-week period. The sensitization exposure involved an injection of 2-butoxyethanol with Freund's adjuvant. The animals were injected behind the shoulders at the beginning of the 1st week of this study. On the 8th day of the study, the animals received a 48-hour topical application of 2-butoxyethanol. The doses for the sensitization exposures were not stated. The guinea pigs were allowed to rest during the 3rd week. On the 24th day of the study, 0.5 mL of a 1% 2-butoxyethanol solution was applied for 48 hours to the left sheared flank using an occlusive patch. The

2. HEALTH EFFECTS

intensity of the erythema and edema was scored, and histopathological examinations were completed 24 hours after the removal of the patch. By this assay, 2-butoxyethanol did not result in dermal sensitization of guinea pigs.

Effects on lymphoreticular organs have been observed in animals after dermal exposure to 2-butoxyethanol. Congestion in the spleen, erythrocytic infiltration, and white atrophic pulp were noted in female New Zealand white rabbits that died after ≥ 72 mg/kg 2-butoxyethanol was applied to their clipped backs for 8 hours (Duprat and Gradiski 1979). Similarly, engorged spleen was noted in rabbits that died after acute dermal doses of ≥ 406 mg/kg (Carpenter et al. 1956). In addition, enlarged spleens were found in female New Zealand rabbits that died after a 6-hour occluded exposure to 902 mg/kg 2-butoxyethanol (Union Carbide 1980a), and dark red spleens were found in male rabbits that died after a 24-hour exposure to 451 mg/kg (Union Carbide 1980b). Gross examination of the thymus, spleen, lymph nodes, and bone marrow did not reveal any adverse effects in guinea pigs treated with a single dermal dose of 2,000 mg/kg and observed for 14 days (Shepard 1994a). The treated area was occluded for 24 hours. No effects on spleen or thymus weight and no histopathological lesions in the spleen, lymph nodes, or thymus were observed in male or female New Zealand rabbits that received dermal doses of ≤ 150 mg/kg/day 2-butoxyethanol 16 hours per day, 5 days per week, for 90 days (CMA 1983). Increased spleen weight, dark spleens, and spleen engorgement effects are probably due to hemolysis, which is discussed under Hematological Effects.

For 2-butoxyethanol acetate, histological examination of spleens revealed no lesions in New Zealand rabbits exposed dermally to doses of $\leq 10,000$ mg/kg for 24 hours (Truhaut et al. 1979).

The highest NOAEL values and all LOAEL values from each reliable study for immunological or lympho-reticular effects in each species and duration category are recorded in Tables 2-6 and 2-7.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after dermal exposure to 2-butoxyethanol or 2-butoxyethanol acetate.

Prostration and narcosis prior to death were noted in female New Zealand white rabbits after 2-butoxyethanol was applied to their clipped backs for 8 hours at ≥ 72 mg/kg (Duprat and Gradiski 1979). Anorexia and lack of spontaneous movement were observed prior to death in New Zealand rabbits given occluded exposure to

2. HEALTH EFFECTS

2,000 mg/kg 2-butoxyethanol for 24 hours on abraded skin (Olin 1976). Muscular flaccidity was also seen in the rabbits at 1,000 and 2,000 mg/kg. Ataxia progressing to moderate-to-marked inactivity and death occurred in pregnant Sprague-Dawley rats treated dermally four times daily with 2-butoxyethanol (0.35 mL per application or 1.4 mL/day) on gestational days 7-16 (Hardin et al. 1984). Female, but not male, New Zealand rabbits receiving a 6-hour occluded dermal application of 902 mg/kg 2-butoxyethanol exhibited nystagmus and convulsions prior to death (Union Carbide 1980a). In an intermediate-duration study, histological examination of the brain and sciatic nerve revealed no pathological lesions in male or female New Zealand rabbits dosed dermally at ≤ 150 mg/kg/day 2-butoxyethanol 6 hours per day, 5 days per week, for 90 days (CMA 1983).

For 2-butoxyethanol acetate, histological examination of the brain revealed no lesions in New Zealand rabbits exposed dermally to $\leq 10,000$ mg/kg for 24 hours (Truhaut et al. 1979).

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Tables 2-6 and 2-7.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after dermal exposure to 2-butoxyethanol or 2-butoxyethanol acetate.

Information regarding reproductive effects in animals after dermal exposure to 2-butoxyethanol or 2-butoxyethanol acetate is limited to data on reproductive organ weights and histological examination of reproductive organs. No studies assessing reproductive function were located. Gross changes at necropsy were not observed in the reproductive organs (epididymides, testes, ovaries, fallopian tubes, uterus, vagina, cervix, uteri) of guinea pigs given a single dermal (24 hours occluded) dose of 2,000 mg/kg and observed for 14 days (Shepard 1994a). No effect on testicular weight was found in male New Zealand white rabbits given dermal applications of 18-361 mg/kg/day 2-butoxyethanol for 6 hours per day for nine applications over 11 days (Union Carbide 1980a). The reproductive organ weights of female rabbits were not determined. Histological examination of testes, epididymides, seminal vesicles, prostate, mammary glands, ovaries, uterus, and vagina revealed no pathological lesions in male or female New Zealand rabbits dosed with 10, 50, or 150 mg/kg/day 2-butoxyethanol for 6 hours per day, 5 days per week for 90 days (CMA 1983). A slight (5.2%), but

2. HEALTH EFFECTS

statistically significant, increase in relative testicular weight was noted for males in the 150-mg/kg/day dose group, but no effects on the weight of the ovaries were found in the females at any dose.

For 2-butoxyethanol acetate, histological examination of the testes and ovaries revealed no pathological lesions in male or female New Zealand rabbits exposed dermally to $\leq 10,000$ mg/kg for 24 hours (Truhaut et al. 1979).

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Tables 2-6 and 2-7.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans after dermal exposure to 2-butoxyethanol or 2-butoxyethanol acetate or regarding developmental effects in animals after dermal exposure to 2-butoxyethanol acetate.

Water or undiluted 2-butoxyethanol was applied four times daily (0.12 mL per application or 0.48 mL/day) on gestational days 7-16 to the shaved interscapular skin of pregnant Sprague-Dawley rats (Hardin et al. 1984). No embryotoxic, fetotoxic, or teratogenic effects were detected in the offspring. At necropsy, no gross malformations were observed in the fetuses

The NOAEL value for developmental effects in rats after acute dermal exposure to 2-butoxyethanol is recorded in Table 2-6.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to 2-butoxyethanol or 2-butoxyethanol acetate. *In vitro* genotoxicity studies are discussed in Section 2.5.-

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to 2-butoxyethanol or 2-butoxyethanol acetate.

2. HEALTH EFFECTS

2.3 TOXICOKINETICS

2-Butoxyethanol is well-absorbed following inhalation, oral, and direct dermal exposure. Dilution with water has resulted in more rapid absorption of 2-butoxyethanol following *in vitro* exposure of rat skin. Small amounts of the vapor can also be absorbed through the skin. There is little information concerning the absorption of 2-butoxyethanol acetate. 2-Butoxyacetic acid has been detected in persons occupationally exposed to 2-butoxyethanol acetate, and the compound was absorbed following direct dermal exposure of rabbits.

Metabolism of 2-butoxyethanol and 2-butoxyethanol acetate to 2-butoxyacetic acid and further metabolism to carbon dioxide is the major pathway of metabolism in both humans and animals. The production of ethylene glycol is a minor pathway of metabolism in both animals and humans. 2-Butoxyethanol and 2-butoxyacetic acid are widely distributed throughout the body, with no site of accumulation identified. Following all routes of exposure, urinary excretion of 2-butoxyacetic acid and its conjugates is the major route of elimination.

2.3.1 Absorption**2.3.1.1 Inhalation Exposure**

Information describing human absorption of 2-butoxyethanol after inhalation exposure comes from both controlled experiments and occupational exposure. Seven male volunteers were exposed to 2-butoxyethanol at the Swedish occupational exposure limit (20 ppm or 0.85 mmol/ m³) for 2 hours during light physical exercise on a bicycle ergometer (Johanson et al. 1986a). Expired air was collected at regular time intervals for estimation of the respiratory uptake of the solvent. Capillary blood was sampled during and after the exposure period and analyzed for 2-butoxyethanol. The respiratory uptake of 2-butoxyethanol averaged 10.1 µmol/minute (1.2 mg/minute) or 57% of the inspired amount. The concentration in blood reached a plateau level of 7.4 µmol/L (0.9 mg/L) within 1-2 hours. In another experimental study in humans, venous blood samples were collected from five healthy male volunteers prior to and after inhalation exposure to 20 ppm 2-butoxyethanol (the Swedish permissible exposure limit) for 2 hours during light physical exercise (Johanson and Johnsson 1991). Samples were collected at 0, 2, 4, and 6 hours from the start of exposure, and analysis indicated that 2-butoxyacetic acid, the major metabolite of 2-butoxyethanol, was found in all

2. HEALTH EFFECTS

samples except those collected prior to exposure. The minimum and maximum observed concentrations of 2-butoxyacetic acid in blood ranged from 20 to 57 μM (2.6-7.5 mg/L) with average concentrations of 22, 44, 39, and 28 μM at 1, 3, 4.9, and 7.1 hours, respectively. The 2-butoxyacetic acid blood level peaked after 2-4 hours.

Healthy male volunteers were exposed to 50 ppm 2-butoxyethanol vapor for 2 hours by mouth through a respiratory valve (Johanson and Boman 1991). Capillary blood samples were collected at regular intervals and analyzed for 2-butoxyethanol. Duplicate experiments were carried out on each volunteer, with normal or increased temperature and humidity. The concentration of 2-butoxyethanol increased during the 1st hour and appeared to approach steady state at about 3 μM during the 2nd hour. The respiratory uptake rate during mouth exposure was 1.3 mmole over a period of 2 hours, or 11 $\mu\text{mol/minute}$.

Seventeen people (2 women and 15 men), who were exposed to glycol ethers in a varnish production plant, were examined to determine their environmental and internal solvent exposure (Angerer et al. 1990). The workers in the production plant (n=12) were exposed to an average 2-butoxyethanol concentration of 1.1 ppm, among other solvents. Internal exposure was estimated by measuring free 2-butoxyethanol in blood as well as free 2-butoxyacetic acid in urine samples. Urine samples were taken pre- and postshift. The exposure of varnish workers to 2-butoxyethanol ranged from <0.1 to 8.1 ppm, compared to <0.1 ppm for workers in the store or the laboratory. The average permissible exposure limit was 20 ppm (Germany). Biological monitoring indicated 2-butoxyethanol levels in postshift blood of 121.3 $\mu\text{g/L}$ for varnish production (range: <5.0-570.0 $\mu\text{g/L}$), compared to 49.4 $\mu\text{g/L}$ for store workers (range: <5.0-143.1 $\mu\text{g/L}$) and <5.0 $\mu\text{g/L}$ for laboratory workers. Pre- and postshift levels of 2-butoxyacetic acid in urine (mg/L) were 3.3 and 10.5 for varnish workers, 2.1 and 4.5 for store workers, and 0.2 and 4.2 for laboratory workers, respectively. Values were not normalized to creatinine. There was little correlation between external and internal levels of exposure, presumably because there was significant direct dermal exposure that was not measured. The study authors indicate that "At these working places glycol ethers were absorbed through the skin on a major scale. Because the workers were cleaning instruments, floor and skin with the solvents, skin contact was far from negligible."

Individual exposure to 2-butoxyethanol acetate was measured by personal air sampling and biological monitoring of urine from 19 employees during an 8-hour workday in four silk-screen printing installations (Johanson et al. 1989). The samples were analyzed by gas chromatography. Urine was quantitatively collected from each subject two or three times during the day. 2-Butoxyethanol acetate was detected in the

2. HEALTH EFFECTS

personal air samples of 5 individuals at an average concentration of 0.44 ppm. Free 2-butoxyacetic acid was detected in the urine of 12 individuals at an average concentration of 8 $\mu\text{mol/L}$.

The data on absorption of 2-butoxyethanol after inhalation exposure in animals is scanty. In an early study, rats, guinea pigs, dogs, and rabbits exposed to 100-400 ppm 2-butoxyethanol for 4 hours excreted 2-butoxyacetic acid in the urine, with most of the metabolite excreted within 24 hours, indicating pulmonary absorption (Carpenter et al. 1956). Dogs and monkeys exposed to 100-398 ppm 2-butoxyethanol for 28-90 days also excreted 2-butoxyacetic acid in the urine.

In a more definitive study, the uptake, metabolism, and excretion of 2-butoxyethanol following 6-hour nose-only inhalation exposure of male Fischer 344 rats was determined at different inhaled concentrations (Sabourin et al. 1992a). Three to five rats per group were exposed to 4.3, 49, or 438 ppm 2-butoxyethanol for 6 hours for the determination of respiratory uptake and excretion. Additional groups of rats were used to determine fractional uptake of inhaled 2-butoxyethanol and body burden at the end of the exposure. Rats selected for body burden determination were euthanized, and the entire carcass was digested at the end of the 6-hour exposure period. Rats selected for metabolism determination were put into metabolism cages following the 6-hour exposure to determine excretion of the compound. The uptake was 4.49 $\mu\text{mol/ppm}$ at 4.3 ppm, 4.58 $\mu\text{mol/ppm}$ at 40 ppm, and 3.58 $\mu\text{mol/ppm}$ at 438 ppm. A less-than-proportional amount of 2-butoxyethanol was inhaled at the high dose because of decreased minute volume.

In a more recent study, eight male Sprague-Dawley rats were exposed to 20 or 100 ppm 2-butoxyethanol 24 hours per day for 1, 2, 3, 4, 6, 8, 10, or 12 days (Johanson 1994). Urine was collected at 24-hour intervals. At the end of the exposure period, animals were killed and blood, muscle, liver, and testis were collected. Blood and tissue samples were analyzed for 2-butoxyethanol and 2-butoxyacetic acid by electron capture gas chromatography. No control group was used. The concentration of 2-butoxyethanol in the four tissues examined increased rapidly during the first 1-3 days of exposure. The average peak concentration of 2-butoxyethanol in the blood was 15.1 $\mu\text{mol/L}$ in the 20-ppm group and 72.3 $\mu\text{mol/L}$ in the 100-ppm group, indicating linear uptake by blood. Respiratory uptake averaged 0.31 mmol/day at 20 ppm and 1.57 mmol/day at 100 ppm, also indicating linear pulmonary uptake at exposure concentrations of ≤ 100 ppm 2-butoxyethanol.

2. HEALTH EFFECTS

2.3.1.2 Oral Exposure

Case reports of intentional poisonings with 2-butoxyethanol provide some kinetic information for human oral exposure. A report on a woman admitted to the hospital after ingestion of 250-500 mL of a window cleaner containing 12% 2-butoxyethanol (467-933 mg/kg 2-butoxyethanol) in a suicide attempt indicated metabolic acidosis, hypokalemia, a rise in serum creatinine level, and markedly increased urinary excretion of oxalate crystals, indicating substantial absorption from the gastrointestinal tract (Rambourg-Schepens et al. 1988). Similar effects have been observed in other case reports of humans who ingested 2-butoxyethanol at 391-650 mg/kg (Bauer et al. 1992; Gijsenbergh et al. 1989). In the case reported by Rambourg-Schepens et al. (1988), kinetic evaluation of urinary excretion of 2-butoxyethanol indicated that 2-butoxyethanol was at the highest level of excretion at 1 day after ingestion.

Studies in animals indicate that absorption of 2-butoxyethanol after oral exposure is rapid and extensive (Ghanayem et al. 1987c). Male Fischer 344 rats were given a single oral dose of [^{14}C]2-butoxyethanol at 125 or 500 mg/kg. Rats were placed in metabolism cages and monitored for 48 hours after treatment. At 48 hours, animals were killed and the ^{14}C -radioactivity in each tissue, as well as in the blood, was determined. Detectable exhalation of radioactivity began 1-2 hours after treatment, indicating rapid absorption and distribution. Approximately 18% and 10% of the administered doses of 125 and 500-mg/kg, respectively, was exhaled as $^{14}\text{CO}_2$ in 48 hours. Cumulative urinary excretion of radioactivity amounted to approximately 32% and 18% of the 125- and 500-mg/kg doses at 8 hours, to approximately 64% and 30% of the respective doses at 24 hours, and to approximately 70% and 40% of the respective doses at 48 hours. Fecal excretion of radioactivity amounted to 2-3% of the doses in 48 hours, and may represent biliary excretion (biliary metabolites were identified, see below) as well as unabsorbed 2-butoxyethanol. Thus, by adding the 48-hour excretion of radioactivity in the expired air and urine, at least 88% of the 125-mg/kg dose and at least 50% of the 500-mg/kg dose were absorbed. The fact that the percentage of radioactivity excreted was less at the higher dose than at the lower dose may indicate saturation of a metabolic pathway rather than lower absorption of the high dose, based on the finding that the urinary levels of the glucuronide conjugate of 2-butoxyethanol of the high-dose rats remained constant for 24 hours, while the glucuronide levels declined after 8 hours in the low-dose rats (see Section 2.3.3 on Metabolism, below).

In male Fischer 344 rats given single gavage doses of 8.6 or 126 mg/kg [^{14}C]2-butoxyethanol, 59% of the low dose of radioactivity and 38-70% of the high dose of radioactivity were excreted in the urine during the first 24 hours (Corley et al. 1994). Excretion of $^{14}\text{CO}_2$ in the expired air amounted to 7.2% of the low-dose

2. HEALTH EFFECTS

and 8% of the high dose in 24 hours. Thus, at least 66.2% of the low dose and 46-78% of the high dose were absorbed.

Male Fischer 344/N rats were allowed access for 24 hours to uniformly labeled [^{14}C]2-butoxyethanol in drinking water at three doses (Medinsky et al. II 990). Elimination of radioactivity was monitored for 72 hours. 2-Butoxyethanol was administered at doses of 290, 860, or 2,590 ppm in drinking water, resulting in consumption of 237, 401, or 1,190 $\mu\text{mol}/\text{kg}$ (28, 47, or 141 $\text{mg}/\text{kg}/\text{day}$). The majority of the ^{14}C was excreted in urine (50-60% of the dose as 2-butoxyacetic acid and 10% as ethylene glycol) or exhaled as CO_2 (8-10% of the dose). Less than 5% of the dose was exhaled as unmetabolized 2-butoxyethanol.

2.3.1.3 Dermal Exposure

Worker exposures to 2-butoxyethanol were evaluated by environmental and biological monitoring for 29 employees in five shops where window-cleaning agents had been used (Vincent et al. 1993). Each of the 29 employees was exposed to 2-butoxyethanol. Eleven men and two women were involved in cleaning cars in four garages. The remaining 16 were office cleaners. Only two of the workers who cleaned new cars wore protective gloves. The study authors suggested that the primary route of exposure was dermal, although some inhalation exposure necessarily occurred. Each of the window-cleaning agents sampled contained 2-butoxyethanol in concentrations ranging from 0.9% to 21.2% in volume. The duration of window-cleaner use ranged from 120 to 320 minutes per day, and quantities of cleaning agents ranged from 220 to 1,200 mL/day for individuals involved in cleaning new cars. The corresponding figures for cleaners of used cars were 20-50 minutes and 50-100 mL. For office cleaners, the corresponding figures were 15 minutes a day and <50 mL of cleaning agent used per day. For cleaners of new cars, the mean 2-butoxyethanol exposure was 2.33 ppm (range, <0.10-7.33 ppm), and the mean urinary 2-butoxyacetic acid concentration in endshift samples was 111.3 mg/g creatinine (range 12.7-371 mg/g creatinine). Mean preshift (average of Monday and Friday) urinary 2-butoxyacetic acid concentration was 17.9 mg/g creatinine (range, <2-98.6 mg/g creatinine). For cleaners of used cars, the mean 2-butoxyethanol exposure was 0.36 ppm (range, <0.10-1.52 ppm), and the mean urinary 2-butoxyacetic acid concentration in endshift samples was 6.3 mg/g creatinine (range, 2-24.4 mg/g creatinine). Mean preshift urinary concentration of 2-butoxyacetic acid was 4.8 mg/kg creatinine (range, 2-33 mg/g creatinine). For the office cleaners, the mean 2-butoxyethanol exposure concentration was 0.32 ppm (range, <0.30-0.73 ppm), and the mean urinary 2-butoxyacetic acid concentration in endshift samples was 2.1 mg/g creatinine (range, 2-3.3 mg/g creatinine). Mean preshift urinary concentration of 2-butoxyacetic acid was 2.1 mg/g creatinine (range, 2-4.6 mg/g

2. HEALTH EFFECTS

creatinine). Correlations of 2-butoxyethanol exposure in air and endshift concentrations of urinary 2-butoxyacetic acid from cleaners of new and used cars (for which the data were most complete) indicated a log-linear relationship. From these results, the study authors estimated that exposure to window cleaners containing 5.7-21.2% 2-butoxyethanol by volume for a period of 160 minutes would result in an endshift urinary 2-butoxyacetic acid concentration of 60 mg/g creatinine. A similar relationship was observed for urinary 2-butoxyacetic acid concentrations and utilization time for office cleaners. The positive correlations between exposure levels of 2-butoxyethanol and 2-butoxyacetic acid in the urine indicate dermal (and probably some pulmonary) absorption of 2-butoxyethanol by these workers.

Experimental evidence exists that dermal absorption of 2-butoxyethanol vapors may contribute to the overall absorption of 2-butoxyethanol during vapor exposure (Johanson and Boman 1991). Healthy male volunteers were exposed to 50 ppm 2-butoxyethanol vapor for 2-hour periods, first by mouth only through a respiratory valve, then by skin only while wearing respiratory protection. Capillary blood samples (finger prick) were collected at regular intervals and analyzed for 2-butoxyethanol. Duplicate experiments were carried out on each volunteer, with normal or increased temperature and humidity. In the mouth-only study, the concentration of 2-butoxyethanol increased during the 1st hour and appeared to approach steady state at about 3 μM during the 2nd hour. The respiratory uptake was 1.3 mmole over 2 hours or 11 $\mu\text{mol}/\text{rminute}$ and the apparent blood clearance was 3.8 L/minute. In the percutaneous exposure, the concentration of 2-butoxyethanol increased to about 9 μM during the 2nd hour. The half-life of 2-butoxyethanol in the blood after skin exposure was about 34 minutes. The average concentration in blood and the calculated rate of uptake of 2-butoxyethanol were about 3-4 times higher during dermal exposure than during inhalation exposure, suggesting that about 75% (45-85%) of the total uptake during normal vapor exposure could be accounted for by dermal absorption. However, the experimental subjects wore only shorts, which is dissimilar from the usual occupational or consumer exposure scenario. In addition, it has been suggested that the finger prick method of blood sampling provides a sample of venous blood draining the skin, rather than a sample of systemic blood (Corley et al. 1997). Therefore, the estimate of dermal absorption by Johanson and Boman (1991) is most likely an overestimate.

A study of 6 men exposed one arm-only to 50 ppm 2-butoxyethanol ($^{13}\text{C}_2$ labeled on the ethylene glycol backbone) for 2 hours, in which blood samples were taken from the unexposed arm, and from a finger prick of the exposed arm, shows much lower dermal absorption of 2-butoxyethanol vapor (Corley et al. 1997) than noted by Johanson and Boman (1991). Concentrations of 2-butoxyethanol in the finger prick sample from the exposed arm were about 1,500 times greater than the blood concentration in the sample from the

2. HEALTH EFFECTS

unexposed arm. Concentrations of 2-butoxyacetic acid were about 37 times greater in the finger prick sample from the exposed arm compared to the sample from the unexposed arm, confirming that the finger prick method of blood sampling provides a sample of venous blood draining the skin. Based on data from the Corley et al. (1997) study and from the Johanson and Boman (1991) study, skin permeability coefficients (k_p) of 2 and 4 cm/hour were estimated for normal (23°C, 29% relative humidity) and elevated (33°C, 71% relative humidity) temperature and relative humidity, respectively. The Corley (1994) model was further refined by modifying it to better reflect human metabolism as measured by urinary metabolite levels in Corley et al (1997), and to include a new permeability coefficient. Dermal uptake was estimated under worst-case resting conditions (respiration rates at their lowest, no clothing worn) and under more realistic conditions (35% of the body surface area exposed). Under the worst case conditions, 15-27% of the total uptake of 2-butoxyethanol vapor would be through the skin, while dermal uptake would be 4.4-8.4% of the total if only 25% of the body surface was exposed. Under simulated exercise (50 W, increased respiratory rates and cardiac output), uptake was estimated as 4.6-8.7% and 1.2-2.3% of the total assuming 100% or 25% of the body surface area was exposed, respectively.

The percutaneous absorption of liquid 2-butoxyethanol was investigated in 12 exposure experiments with five men (Johanson et al. 1988). All were nonsmokers and stated low or no consumption of alcohol. None had been exposed to industrial solvents. All had participated in a previous study of 2-butoxyethanol (Johanson et al. 1986a). The subjects kept two or four fingers immersed in neat 2-butoxyethanol for 2 hours. Capillary blood samples were collected from the other hand before, during, and up to 4 hours after the exposure and analyzed for 2-butoxyethanol. The presence of 2-butoxyethanol in blood and 2-butoxyacetic acid in urine confirmed that 2-butoxyethanol enters the systemic circulation in human males during *in vivo* dermal exposure. The shape of the uptake profile varied considerably among individuals and also among experiments. Percutaneous uptake rates were calculated from measured blood levels of 2-butoxyethanol with the use of kinetic parameters (clearance and volume of distribution) obtained in earlier experiments with the same subjects. The uptake rates ranged from 7 to 96 nmol/minute/cm² (0.83- 1.35 mg/minute/cm²), with a geometric mean of 20 nmol/minute/cm² (2.36 mg/minute/cm²). The results indicate that persons exposing large portions of their skin to 2-butoxyethanol are likely to absorb significant doses.

An *in vitro* study indicated that 2-butoxyethanol is absorbed through human abdominal epidermis (Dugard et al. 1984). Undiluted 2-butoxyethanol was applied to human abdominal epidermal membranes for a period of 8 hours. The absorption rate was 0.2 mg/cm²/hour. In another *in vitro* study, a 10% solution of 2-butoxyethanol was applied to a 3- cm² area on frozen human arm skin, which was obtained at autopsy,

2. HEALTH EFFECTS

under semioclusive or nonocclusive conditions (Bartnik et al. 1987). The percentage of absorption was 6.9% for the nonocclusive condition and 17.3% for the semioclusive condition.

2-Butoxyethanol is also absorbed by animal skin. 2-Butoxyethanol was applied to the shaven skin of male and female rats on a 12- cm² area at a dose of 200 mg/kg (Bartnik et al. 1987). The application site was protected with a glass capsule to prevent oral uptake. Urine was collected at intervals of 0-8, 8-24, and 24-48 hours following application and stored at -80°C. Total radioactivity was determined for urine, cage rinse water, skin, and glass capsule. Percutaneous absorption was assessed by using the measurements of urinary excretion of ¹⁴C from 0 to 48 hours following cutaneous application of 2-butoxyethanol. Radioactivity measured during the 48 hours following cutaneous application of radiolabeled 2-butoxyethanol showed that 20-23% of the applied dose was found in the urine, including cage rinse water, with no notable differences by sex. Over 95% of the radioactivity excreted in the urine was eliminated during the first 24 hours (metabolite not identified). Small amounts of radioactivity were found on the treated skin of male (4.7%) and female (8.3%) rats. Percutaneous absorption was determined to be 25-29% of the applied dose.

Percutaneous absorption was measured after three different doses of the [¹⁴C]2-butoxyethanol (61, 181, or 299 mg/kg) were applied to same-sized areas on the clipped backs of Fischer 344/N rats; the sites of application were nonoccluded but were protected with a perforated covering (Sabourin et al. 1992b, 1993). The rates of excretion of the ¹⁴C-labeled parent compound and metabolites by different routes were measured, as well as the amount of ¹⁴C remaining in the carcass. Within the dose range studied, the absorption and metabolism of 2-butoxyethanol by Fischer 344/N rats was linearly related to the dermally applied dose. The absorption was approximately 21-26%, regardless of the dose administered. A small fraction of the applied dose (0.3-2%) was still present at the application site 72 hours following dosing, representing unabsorbed parent compound, dermally excreted parent compound, or metabolites in the skin. The remainder of the applied dose was recovered as volatilized radioactivity. The total recovery was 78-90%. The majority of the absorbed dose was excreted in the urine. Peak levels of radioactivity were reached at about 1 hour, with a half-life of about 4 hours.

The percutaneous absorption rate and elimination kinetics of 2-butoxyethanol were estimated in the guinea pig (Johanson and Femstrom 1986). An intravenous bolus dose of 5 or 11 mg/kg was administered into the jugular vein of 10 pentobarbital-anesthetized animals in order to calculate total clearance and mean residence time of the compound in guinea pigs. Following the intravenous dose, the apparent total clearance and mean residence time of 2-butoxyethanol in the blood were calculated to be 128 mL/minute/kg and 4.7 minutes,

2. HEALTH EFFECTS

respectively. At 2.5 hours after the intravenous dose, which was sufficient time for clearance of the intravenous dose, 1 mL neat 2-butoxyethanol was applied in two sealed glass rings on the clipped back of the animal for 2 hours. The concentration of 2-butoxyethanol in blood rose rapidly following the dermal application, and then approached a plateau level of 21 $\mu\text{mol/L}$ (2.482 mg/L) during the latter half of the exposure period. The absorption rate through the skin was estimated to be 0.25 (range, 0.05-0.46) $\mu\text{mol/minute/cm}^2$ (29.6 $\mu\text{g/minute/cm}^2$). The percutaneous uptake rate of 2-butoxyethanol in the present study was comparable to that obtained *in vitro* with human skin (i.e., 0.03 $\mu\text{mol/minute/cm}^2$ [3.55 $\mu\text{g/minute/cm}^2$]) once species differences were taken into account. The time lag of 21-60 minutes observed in the present study is in accordance with that reported for the penetration of 2-butoxyethanol through human skin *in vitro* (Dugard et al. 1984).

In *in vitro* experiments, frozen human skin from the flexus side of arms (obtained at autopsy), fresh dorsal skin of hairless rats, and frozen dorsal skin of pigs were used in a comparison absorption study of 2-butoxyethanol (Bartnik et al. 1987). Connective tissues and fat were removed. The solutions of [^{14}C]2-butoxyethanol were applied to a skin area of 3 cm^2 for human skin and 5 cm^2 for animal skin for 1 hour. The solutions (30 μL) of 2-butoxyethanol administered were as follows: 100% 2-butoxyethanol; 3.5% 2-butoxyethanol in water; 10% 2-butoxyethanol in water; 3.5% or 10% 2-butoxyethanol with 5% linear sodium dodecylbenzene sulfonate (LAS) in water; and 3.5% or 10% 2-butoxyethanol with 5% isopropanol in water. Both semiocluded and nonocclusive conditions were used. Absorption was determined after exposure durations of 1, 6, and 16 hours (semioclusive) in rat skin 6 hours (semioclusive) in pig skin, and 1 hour nonocclusive in rat skin. 2-Butoxyethanol at 3.5% (0.21 mg/cm^2) in water was also tested after 10, 30, and 60 minutes under nonocclusive conditions in both rat and pig skin. Absorbed and nonabsorbed radioactivity levels were determined. In rat skin under semioclusion, the applied dose of 2-butoxyethanol was rapidly absorbed (19% of 100% 2-butoxyethanol, 62.7% of 10% 2-butoxyethanol, and 45.6% of 3.5% 2-butoxyethanol in water at 1 hour) and after 16 hours was almost completely absorbed through the skin (94.3% of 100% solution, 82.6% of 10% solution, and 88.4% of 3.5% solution). The amount of penetration depended on time as well as concentration. The penetration of pure 2-butoxyethanol was initially slower than from aqueous solutions, but was more complete after 16 hours. In nonoccluded rat skin, 5.6% of the 100% 2-butoxyethanol, 10.4% of the 10% solution, and 11.1% of the 3.5% solution were absorbed within 1 hour. In pig skin under semioclusion, the applied dose of 2-butoxyethanol was less rapidly absorbed (2-3 times slower) than through rat skin. The penetration of pure 2-butoxyethanol was slower than from aqueous solutions and reached 11.2% after 6 hours, compared with 36.9% of the 10% solution and 47.5% of the 3.5% solution of 2-butoxyethanol. Isopropanol and LAS had little effect on absorption. In nonoccluded skin

2. HEALTH EFFECTS

treated with 3.5% 2-butoxyethanol, rat skin absorbed 10.4% in 10 minutes, 11.5% in 30 minutes, and 11.0% in 60 minutes, while pig skin absorbed 2.8% at 10 minutes, 6.6% at 30 minutes, and 5.4% at 60 minutes. In the comparison of *in vitro* skin penetration for humans, rats, and pigs, the data for 100 $\mu\text{g}/\text{cm}^2$ exposure for 1 hour were presented. For nonocclusive exposure, the percentages of absorption were 11% for rat skin, 8.6% for pig skin, and 6.9% for human skin. For semioclusive exposure, the percentages of absorption were 43.3% for rat skin, 17.7% for pig skin, and 17.3% for human skin. Thus, the absorption pattern was: hairless rat >>> pig \geq human skin.

In a study on 2-butoxyethanol acetate in groups of six New Zealand rabbits to which the compound was applied dermally under occlusion for 24 hours, the doses of 3,319, 3,957, 4,766, 5,957, and 10,000 mg/kg were reported to correspond to absorbed doses (mg/kg \pm SE) of 610 \pm 310, 910 \pm 140, 1,130 \pm 390, 1,830 \pm 290, and 2,200 \pm 530 mg/kg, respectively (Truhaut et al. 1979). The absorbed doses were determined by comparing the amount of 2-butoxyethanol acetate applied under occlusion with the amount of 2-butoxyethanol acetate remaining after 24 hours of contact with the skin. The absorbed doses showed wide variability, which may be because this method is not very accurate.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Some information describing distribution of 2-butoxyethanol and its major metabolite, 2-butoxyacetic acid after human inhalation exposure can be found in reports of controlled experiments. Venous blood samples were collected from five healthy male volunteers prior to and after inhalation exposure to 20 ppm 2-butoxyethanol during light physical exercise for 2 hours (Johanson and Johnsson 1991). 2-Butoxyacetic acid was found in all blood samples except those collected prior to exposure. Binding of 2-butoxyacetic acid to blood components is indicated by the low apparent volume of distribution of approximately 15 L, which is approximately equal to the volume of extracellular water, and the fact that the renal clearance rate is about one-third of the glomerular filtration rate. In another human study, seven male volunteers were exposed to 2-butoxyethanol for 2 hours at 20 ppm during light physical exercise on a bicycle ergometer (Johanson et al. 1986a). For 2-butoxyethanol, the apparent value of steady-state volume of distribution was 54 L and the mean residence time was 42 minutes. 2-Butoxyethanol was no longer detectable in the blood 2-4 hours after the end of exposure (Johanson et al. 1986a).

2. HEALTH EFFECTS

In animal studies, the body burden of [^{14}C]2-butoxyethanol following 6-hour nose-only inhalation exposure of male Fischer 344 rats was determined at several inhaled concentrations (Sabourin et al. 1992a). The uptake (4.49 $\mu\text{mol/ppm}$ at 4.3 ppm; 4.58 $\mu\text{mol/ppm}$ at 49 ppm; 3.58 $\mu\text{mol/ppm}$ at 438 ppm) and metabolism (0.79 $\mu\text{mol/ppm}$ at 4.3 ppm; 0.95 $\mu\text{mol/ppm}$ at 49 ppm; 0.88 $\mu\text{mol/ppm}$ at 438 ppm) of 2-butoxyethanol, expressed as [^{14}C]2-butoxyethanol equivalents, were essentially linear up to 438 ppm. Most (greater than 80%) of the [^{14}C]2-butoxyethanol-derived material in blood was in the plasma. 2-Butoxyacetic acid was the major metabolite of 2-butoxyethanol in plasma. Ratios of ethylene glycol to 2-butoxyacetic acid in plasma were higher than those in urine. The 2-butoxyethanol-derived ^{14}C in plasma rapidly became associated with the acid-precipitable (protein) fraction, probably because of binding of metabolites to proteins or incorporation of the 2-butoxyethanol metabolites into the carbon pool.

In a more recent study, eight male Sprague-Dawley rats were exposed to 20 or 100 ppm 2-butoxyethanol 24 hours per day for 1, 2, 3, 4, 6, 8, 10, or 12 days (Johanson 1994). Urine was collected at 24-hour intervals. At the end of the exposure period, animals were killed and blood, muscle, liver, and testis were collected. Blood and tissue samples were analyzed for 2-butoxyethanol and 2-butoxyacetic acid by electron capture gas chromatography. The concentrations of 2-butoxyethanol in blood, in the 20-ppm group were as follows: 7.5-29.0 $\mu\text{mol/L}$, with an average of 15.1 $\mu\text{mol/L}$; muscle, 0.9-13.0 $\mu\text{mol/kg}$, average of 9.1 $\mu\text{mol/kg}$; testis, 1.3-11.6 $\mu\text{mol/kg}$, with an average of 3.9 $\mu\text{mol/kg}$; and liver 5.1-16.4 $\mu\text{mol/kg}$, with an average of 10.8 $\mu\text{mol/kg}$. In the 100-ppm group, the concentrations were as follows: blood, 23.0-103 $\mu\text{mol/L}$, with an average of 72.3 $\mu\text{mol/L}$, muscle, 13.6-49.8 $\mu\text{mol/kg}$, with an average of 30.4 $\mu\text{mol/kg}$; testis, 4.7-36.1 $\mu\text{mol/kg}$, average, with an average of 12.6 $\mu\text{mol/kg}$; and liver, 42.4-129 $\mu\text{mol/kg}$, with an average of 83.8 $\mu\text{mol/kg}$. Although data points were reported on exposure days 1-12, the averages were calculated for 2-12 exposure days. The concentration of 2-butoxyethanol increased rapidly in the tissues during days 1-3 and continued to increase, but more slowly, during the remaining days. Tissue concentrations in the 100-ppm group conformed to expected linear kinetics. Concentration ratios (100 ppm/20 ppm) were 5.1 for blood, 3.5 for muscle, 3.6 for testis, and 7.5 for liver. The kinetic pattern of 2-butoxyacetic acid was similar to 2-butoxyethanol. The concentrations in the 20-ppm group were as follows: blood, 31.8-48.8 $\mu\text{mol/L}$, with an average of 41.0 $\mu\text{mol/L}$; muscle, 5.8-14.9 $\mu\text{mol/kg}$, with an average of 9.3 $\mu\text{mol/kg}$; testis, 9.7-23.3 $\mu\text{mol/kg}$, with an average of 14.1 $\mu\text{mol/kg}$; and liver, 9.5-26.4 $\mu\text{mol/kg}$, with an average of 16.4 $\mu\text{mol/kg}$. In the 100-ppm group, the concentrations were as follows: blood, 125-226 $\mu\text{mol/L}$, with an average of 179 $\mu\text{mol/L}$; muscle, 17.9-63.6 $\mu\text{mol/g}$, with an average of 36.2 $\mu\text{mol/kg}$; testis, 11.6-48.5 $\mu\text{mol/kg}$, with an average of 26.7 $\mu\text{mol/kg}$; and liver, 52.8-107 $\mu\text{mol/kg}$, with an average of 85.2 $\mu\text{mol/kg}$. Again, the data points were reported on exposure

2. HEALTH EFFECTS

days 1-12, but the averages were calculated for 2-12 exposure days. As with 2-butoxyethanol, the 2-butoxyacetic acid concentration increased rapidly in the tissues during the first 1-3 days and then more slowly during the remaining days. Tissue concentrations in the 100-ppm group conformed to expected linear kinetics. Concentration ratios (100 ppm/20 ppm) were 4.4 for blood, 4.7 for muscle, 2.3 for testis, and 5.3 for liver. Thus, the disposition of 2-butoxyethanol and 2-butoxyacetic acid was linear at the exposure concentrations used, and although the number of tissues examined was limited, the data indicated extensive distribution.

2.3.2.2 Oral Exposure

Studies in animals indicate that distribution of 2-butoxyethanol after oral exposure is rapid (Ghanayem et al. 1987c). Male Fischer 344 rats were given a single oral dose of [¹⁴C]2-butoxyethanol of 125 or 500 mg/kg. Rats were placed in metabolism cages and monitored for 48 hours after treatment. At 48 hours, animals were killed and the ¹⁴C -radioactivity in each tissue, as well as in the blood, was determined. Tissue distribution of 2-butoxyethanol revealed that 2-butoxyethanol is distributed to all tissues, with the highest levels (determined 48 hours after dosing) detected in the forestomach (654 nmol/g at 125 mg/kg and 7,606 nmol/g at 500 mg/kg). The increase in the tissue concentration in rats treated with 500 mg/kg (as compared to that in rats treated with 125 mg/kg) was not proportional to the increase in dose. While the ratio of the administered doses was 1:4, the ratio of the tissue concentration in most tissues was greater than 1: 10. This may be related to saturation of 2-butoxyethanol metabolism at the high dose. There seems to be a positive correlation between tissue levels and the tissues exhibiting toxicity. Other levels were as follows: liver, 107 nmol/g at 125 mg/kg and 1,666 nmol/g at 500 mg/kg; skin, 75 nmol/g at 125 mg/kg and 806 nmol/g at 500 mg/kg; kidney, 69 nmol/g at 125 mg/kg and 1,304 nmol/g at 500 mg/kg; lung, 68 nmol/g at 125 mg/kg and 1,352 nmol/g at 500 mg/kg; the glandular stomach, 61 nmol/g at 125 mg/kg and 1,743 nmol/g at 500 mg/kg; spleen, 54 nmol/g at 125 mg/kg and 1,149 nmol/g at 500 mg/kg; fat, 40 nmol/g at 125 mg/kg and 162 nmol/g at 500 mg/kg; heart, 36 nmol/g at 125 mg/kg and 927 nmol/g at 500 mg/kg; blood, 34 nmol/g at 125 mg/kg and 1,288 nmol/g at 500 mg/kg; testes, 22 nmol/g at 125 mg/kg and 659 nmol/g at 500 mg/kg; and muscle, 17 nmol/g at 125 mg/kg and 571 nmol/g at 500 mg/kg.

In a companion study in male Fischer 344 rats, 2-butoxyethanol was given orally by gavage at 500 mg/kg alone or after pretreatment with pyrazole, which was found to inhibit the metabolism of 2-butoxyethanol to 2-butoxyacetic acid (Ghanayem et al. 1987b) (see Section 2.3.3). The levels of 2-butoxyethanol in tissues measured 48 hours after dosing with 2-butoxyethanol alone were those reported above by Ghanayem et al.

2. HEALTH EFFECTS

(1987c) for the 500-mg/kg dose. In rats pretreated with pyrazole followed by 500 mg/kg [¹⁴C]2-butoxyethanol, the levels of 2-butoxyethanol-derived radioactivity in these tissues were appreciably lower: 2,384 nmol/g in forestomach, 417 nmol/g in liver, 144 nmol/g in skin, 282 nmol/g in kidney, 231 nmol/g in lung, 380 nmol/g in glandular stomach, 303 nmol/g in spleen, 120 nmol/g in fat, 102 nmol/g in heart, 135 nmol/g in blood, 104 nmol/g in testes, and 65 nmol/g in muscle (Ghanayem et al. 1987b). Analysis of radioactivity in the liver revealed that 2-butoxyacetic acid was the only radioactive species. These observations, along with the effects of pyrazole on the metabolic pathway (see Section 2.3.3) and excretion (see Section 2.3.4.2) of 2-butoxyethanol, indicated that pyrazole enhanced the elimination of 2-butoxyethanol and protected the rats from its hematotoxic effects.

2.3.2.3 Dermal Exposure

Three different amounts of the [¹⁴C]2-butoxyethanol (61, 181, or 299 mg/kg) were applied to same-sized areas on the clipped backs of Fischer 344/N rats, and nonoccluded percutaneous absorption was measured (Sabourin et al. 1992b, 1993). A small amount of the applied dose (0.3-2%) was still present at the application site 72 hours following dosing, representing unabsorbed parent compound, absorbed parent compound, or metabolites in the skin. The majority of the absorbed dose was excreted in the urine. At 72 hours, 7-16% of the absorbed radioactivity remained in the carcass. Over 80% of the blood radioactivity was associated with the plasma, and less than 20% was associated with the red blood cells.

2.3.2.4 Other Routes of Exposure

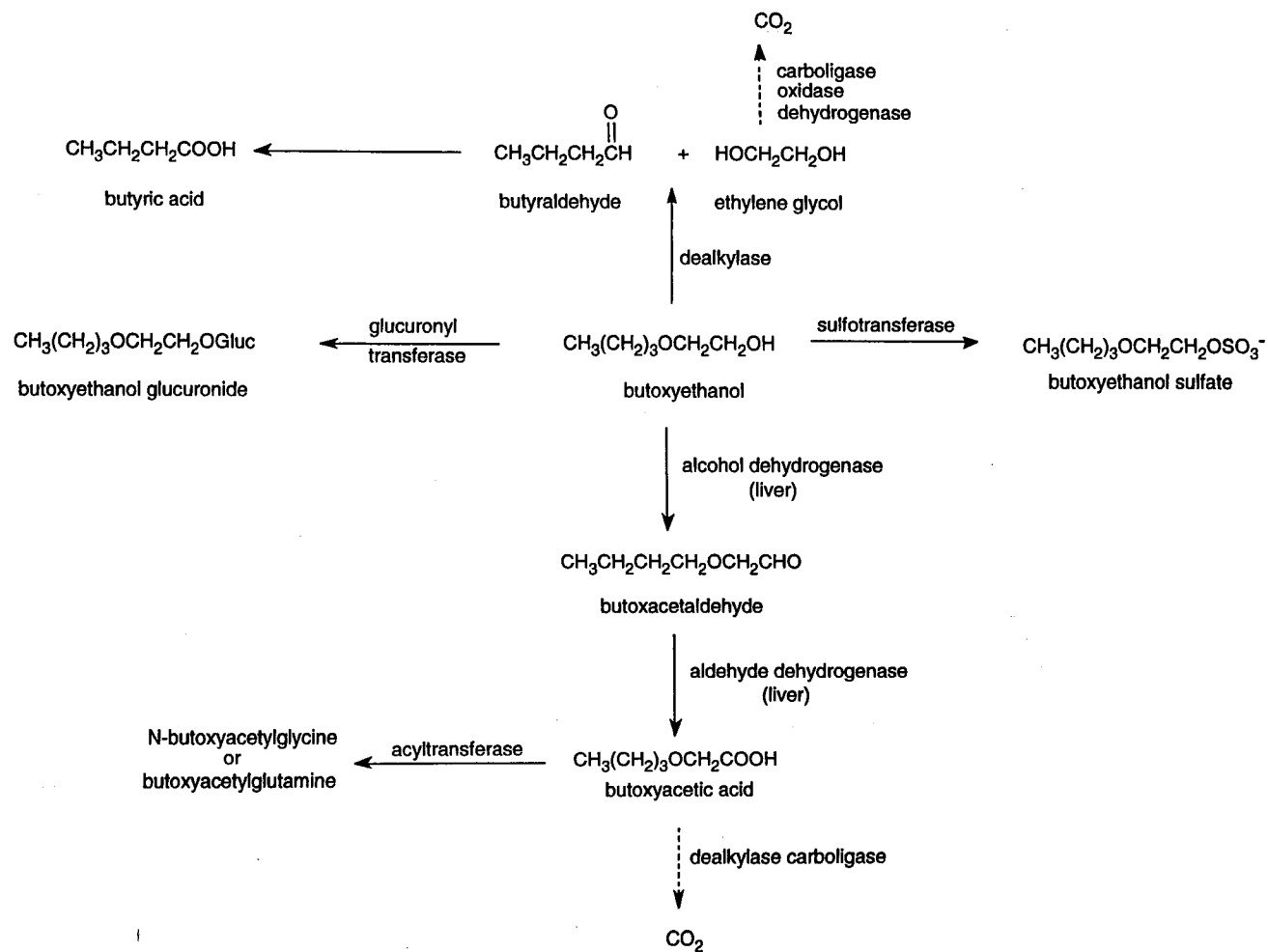
After injection of male Wistar rats in the scapular region with a single subcutaneous dose of 118 mg/kg [¹⁴C]2-butoxyethanol, not exceeding 99 μ Ci/kg, the tissue distribution of radioactivity was determined (Bartnik et al. 1987). With the exception of plasma, all organs showed a higher relative specific radioactivity than blood 72 hours after dosing. If the specific radioactivity found in blood is given a value of 1, values for specific radioactivity (relative to blood) were as follows: 3.02 in liver, 1.99 in kidney, 6.62 in spleen, 1.55 in testis, 7.39 in thymus, 0.93 in plasma, 1.14 in carcass, 2.74 in fat, and 1.25 in sternum. However, the percentages of the applied dose of radioactivity in these tissues were reported to be 0.49% in liver, 0.07% in kidney, 0.06% in spleen, 0.08% in testis, 0.06% in thymus, 0.16% in plasma, 4.05% in carcass, and 1.60% in fat. The percentage of applied radioactivity in blood was 0.32%. The percentage of applied radioactivity in the sternum was not calculated.

2. HEALTH EFFECTS

2.3.3 Metabolism

There is no available evidence to suggest that the route of administration has any substantial effect on the subsequent metabolism of 2-butoxyethanol in humans. However, data from animals indicate that route of exposure may make some difference in the relative amounts of metabolites produced (Medinsky et al. 1990; Sabourin et al. 1992a, 1992b, 1993). Data regarding metabolism of 2-butoxyethanol have been obtained from a large volume of work done on other glycol ethers with specific experiments carried out on 2-butoxyethanol (summarized in EPA 1984; Miller 1987; NIOSH 1990). The metabolic scheme for 2-butoxyethanol is shown in Figure 2-6. 2-Butoxyethanol is oxidized in the liver by alcohol dehydrogenase to butoxy-acetaldehyde, which is further oxidized to 2-butoxyacetic acid by acetaldehyde dehydrogenase. In animals and humans, 2-butoxyacetic acid can be conjugated with glycine to form *N*-butoxyacetylglucine, or it can be broken down to CO₂ (Ghanayem et al. 1987b; Marxhall 1982; Medinsky et al. 1990; Rettenmeier et al. 1993). 2-Butoxyethanol can also be dealkylated by CYP2E1 to form ethylene glycol and butyraldehyde; ethylene glycol is then broken down to oxalic acid and ultimately to CO₂. Rettenmeier et al. (1993) identified an additional amino acid conjugate, *N*-butoxyacetylglutamine, in human urine samples, which accounted for an average of 50% of the total 2-butoxyacetic acid detected; the remainder was free. The formation of the *N*-butylacetylglutamine conjugate in humans has been confirmed in humans exposed (one arm only) to 2-butoxyethanol; 213 of total urinary 2-butoxyacetic acid was conjugated with glutamine (Corley et al. 1997). In rats, 2-butoxyethanol can also be detoxified by conjugation with sulfate to form butoxyethanol sulfate, or with glucuronic acid to form the glucuronide (Ghanayem et al. 1987b; Ghanayem et al. 1987c). Clinical reports and animal experiments that have contributed to the elucidation of this metabolic scheme are described below. Corley et al (1997) found no free or conjugated ethylene glycol or its metabolite, glycolic acid, in the urine.

A report on a woman admitted to the hospital after ingestion, in a suicide attempt, of 250-500 mL, of a window cleaner containing 12% (467-933 mg/kg) 2-butoxyethanol indicated that metabolic acidosis, hypokalemia, a rise in serum creatinine level, and a markedly increased urinary excretion of oxalate crystals were observed, suggesting a metabolic pattern after absorption from the stomach (Rambourg-Schepens et al. 1988). The high output of the oxalate in the urine was explained by the metabolism of 2-butoxyethanol to ethylene glycol, which was further metabolized to oxalic acid. This assumption was supported by the existence of metabolic acidosis coincidental with the urinary peak oxalate level; however, 2-butoxyacetic acid can also cause metabolic acidosis. Similar metabolic effects have been reported by others (Bauer et al. 1992; Gijsenbergh et al. 1989).



*Derived from the work of Ghanayem et al. 1987b; Marshall 1982; Medinsky et al. 1990

2. HEALTH EFFECTS

Venous blood samples were collected from five healthy male volunteers prior to and after inhalation exposure to 20 ppm 2-butoxyethanol (the Swedish permissible exposure limit) for 2 hours under light physical exercise (Johanson and Johnsson 1991). Blood samples were collected at 0, 2, 4, and 6 hours from the start of exposure and analyzed by gas chromatography. The minimum and maximum observed concentrations of free 2-butoxyacetic acid in blood ranged from 20 to 57 μM (2.6-7.5 mg/L) with average concentrations of 22, 44, 39, and 28 μM at 1, 3, 4.9, and 7.1 hours, respectively. Free 2-butoxyacetic acid was found in all samples except those collected prior to exposure. These concentrations were about two orders of magnitude lower than those causing swelling and hemolysis of human erythrocytes *in vitro* (Ghanayem 1989). The 2-butoxyacetic acid blood level peaked after 2-4 hours. The decrease between 4-6 hours indicates an average half-time of 2-butoxyacetic acid in blood of about 4 hours, which is in accordance with half-times in urine observed by Johanson et al. (1986a) in humans similarly exposed (see Section 2.3.4.1). An interfering peak with a retention time similar, but not identical, to 2-butoxyacetic acid was found in all samples with the area of the peak corresponding to 1.8 μM 2-butoxyacetic acid. 2-Butoxyacetic acid was also detected in the urine of seven male subjects exposed to 20 ppm of 2-butoxyethanol for 2 hours (Johanson et al. 1986a). These subjects excreted 15.2-55% of the respiratory uptake in the urine.

The effect of genetic polymorphism of CYP 2E1 was studied in 32 male workers exposed to 2-butoxyethanol (Haufrond et al. 1997). Only one worker expressed the c2 allele (heterozygote c1/c2), while the other 30 workers were homozygous for c1. The heterozygous worker was the only worker for whom urinary 2-butoxyethanol acid was similar before and after his work shift, although he was exposed to 0.53 ppm 2-butoxyethanol. The study author indicated that the reduced 2-butoxyacetic acid excretion in their heterozygous subject was likely a result of increased activity of the c2 compared to the c1 allele; however, no firm conclusions can be drawn since only free 2-butoxyacetic acid was measured and it is therefore unknown how much conjugated 2-butoxyacetic acid was in the urine.

In an early study, rats, guinea pigs, dogs, and rabbits exposed to 100-400 ppm 2-butoxyethanol for 4 hours excreted free 2-butoxyacetic acid in the urine (Carpenter et al. 1956). Dogs and monkeys exposed to 100-398 ppm 2-butoxyethanol for 28-90 days also excreted free 2-butoxyacetic acid in the urine. These data indicate that the metabolism of 2-butoxyethanol to 2-butoxyacetic acid is a common pathway in mammalian species.

Other studies in animals also indicate that 2-butoxyethanol is metabolized to 2-butoxyacetic acid (Ghanayem et al. 1987c). Male Fischer 344 rats were given a single oral dose of [^{14}C]2-butoxyethanol at 125 or

2. HEALTH EFFECTS

500 mg/kg. Rats were placed in metabolism cages and monitored for 48 hours after treatment. Urine, feces, and bile were collected for metabolite analysis. Urinary metabolites detected at any one time point included free 2-butoxyacetic acid as the primary constituent (74-100%), the 2-butoxyethanol-glucuronide (0-24%), and a minor amount of the 2-butoxyethanol-sulfate conjugate (0-3%) detected only at the lower dose. In the animals treated with 500 mg/kg 2-butoxyethanol, a larger proportion of the administered dose was detected as the glucuronide, suggesting that the enzymes were saturated in the high-dose animals. In the bile, flow increased significantly at 0.5 hour after treatment and remained above pretreatment levels for the following 4 hours. Biliary metabolites included free 2-butoxyacetic acid, the 2-butoxyethanol-glucuronide, and the parent compound. The parent compound was detected only in the first 2 hours after treatment. In contrast to the urine, the 2-butoxyethanol-glucuronide was the major metabolite in the bile, while 2-butoxyacetic acid increased with time at the expense of the glucuronide.

In studies designed to investigate the metabolic basis of 2-butoxyethanol-induced hematotoxicity in male Fischer 344 rats, treatment with pyrazole, an alcohol dehydrogenase inhibitor, protected the rats against 2-butoxyethanol hematotoxicity and prevented the metabolism of 2-butoxyethanol to 2-butoxyacetic acid (Ghanayem et al. 1987b). Inhibition of 2-butoxyethanol metabolism to 2-butoxyacetic acid was accompanied by an increase in the production of the glucuronide and sulfate conjugates of 2-butoxyethanol. Rats treated with pyrazole and 2-butoxyethanol exhibited a 10-fold decrease in the proportion of free urinary 2-butoxyacetic acid to 2-butoxyethanol-glucuronide and 2-butoxyethanol-sulfate (total production), compared to rats treated with 2-butoxyethanol alone. Pretreatment of rats with cyanamide, an aldehyde dehydrogenase inhibitor, also protected the animals against the hematotoxicity and modified 2-butoxyethanol metabolism in a manner similar to that with pyrazole. Further experiments indicated that hematotoxicity could result from treatment with 2-butoxyethanol, the metabolic intermediate butoxyacetaldehyde, or the ultimate toxic metabolite 2-butoxyacetic acid. Cyanamide also served to protect from the butoxyacetaldehyde-induced toxicity. Pyrazole significantly increased bile flow, even more than 2-butoxyethanol alone, and excretion of radioactivity from 2-(1-[¹⁴C]butoxy)ethanol in bile was higher in rats pretreated with pyrazole (16%) than in rats given 2-butoxyethanol alone (8%). The composition of biliary metabolites also differed in animals treated with 2-butoxyethanol alone compared with animals treated with 2-butoxyethanol in conjunction with pyrazole. Free 2-butoxyacetic acid constituted 10%, 21%, and 46% of the total radioactivity excreted in the bile at 0-1, 2-4, and 6-8 hours, respectively, after dosing with 2-butoxyethanol alone. In contrast, no 2-butoxyacetic acid was detected in any bile fractions from animals treated with pyrazole. In these rats, approximately 12% of the radioactivity was excreted in the 1st hour as unchanged 2-butoxyethanol, with the remaining portion being the glucuronide. No other metabolites were detected in the bile. Further evidence of

2. HEALTH EFFECTS

the requirement for metabolic activation prior to the onset of hematotoxicity was observed with the administration of deuterium-labeled 2-butoxyethanol. The onset of hematotoxicity was significantly delayed, indicating the slower oxidation of 2-butoxyethanol due to the deuterium substitution in place of the somewhat smaller hydrogen atoms. This study provided conclusive evidence of the following: there is a good correlation between the 2-butoxyethanol-induced hematotoxicity and the amount of free 2-butoxyacetic acid in the urine; alcohol and aldehyde dehydrogenase are essential to the metabolic activation of 2-butoxyethanol to 2-butoxyacetic acid; and hematotoxicity induced by 2-butoxyethanol can be attributed to its metabolite, 2-butoxyacetic acid.

Experiments designed to determine the effect of age on the toxicity and metabolism of 2-butoxyethanol indicate that in rats, young animals (4-5 weeks old) are more resistant to the toxic effects than are older rats (9-13 weeks old) receiving an equivalent dose (Ghanayem et al. 1987a). Young rats excreted less free 2-butoxyacetic acid than adult rats, and more 2-butoxyethanol-glucuronide. No sulfate conjugate of 2-butoxyethanol was detected in the urine of young rats. High-performance liquid chromatographic analysis of the urinary metabolites of 2-butoxyethanol in adult and young rats showed that the ratio of free 2-butoxyacetic acid to the total amount of the glucuronide and sulfate conjugates of 2-butoxyethanol (previously thought to reflect an activation/detoxification index of 2-butoxyethanol) was significantly higher in older rats. An unknown metabolite was found in the urine of both young and adult rats in amounts of 6-8% and 1%, respectively. Additional studies on the effect of dose, age, and inhibition of metabolism on the toxicity of 2-butoxyethanol indicated that total metabolism was dose dependent, but there was no effect of dose on half-life or volume of distribution (Ghanayem et al. 1990a). There was no effect of age on half-life, volume of distribution, or clearance of 2-butoxyethanol. Inhibition of metabolism of 2-butoxyethanol with pyrazole (inhibition of alcohol dehydrogenase) or cyanamide (inhibition of aldehyde dehydrogenase) significantly increased the half-life and decreased the clearance. Although pyrazole had no effect on volume of distribution, cyanamide pretreatment caused a decrease in the volume of distribution for 2-butoxyethanol; the reason for this was not clear. Analysis of toxicokinetic parameters of free 2-butoxyacetic acid indicated that the half-life and maximum plasma concentration were directly related to the age of the animals and the dose of 2-butoxyethanol. Pyrazole decreased the maximum plasma concentration and half-life of free 2-butoxyacetic acid, presumably because of inhibition of metabolism of 2-butoxyethanol. Cyanamide increased the half-life and decreased the plasma concentration of free 2-butoxyacetic acid. The study authors noted that the effects of cyanamide are probably related to the inhibition of the conversion of butoxyacetaldehyde to 2-butoxyacetic acid, but the reason that cyanamide increased the half-life of 2-butoxyacetic acid is unclear. Probenecid, an inhibitor of renal transport of organic acids, did not alter the plasma concentration,

2. HEALTH EFFECTS

volume of distribution, or clearance of free 2-butoxyethanol, but it did increase the half-life of free 2-butoxyacetic acid.

In an effort to identify underlying mechanisms associated with the development of tolerance to the hemolytic effects of 2-butoxyethanol, male Fischer 344 rats were treated with 125 mg/kg/day of unlabeled 2-butoxyethanol for 3 or 7 days by gavage followed by a single dose of 125 mg/kg of [^{14}C]2-butoxyethanol (40-50 $\mu\text{Ci/kg}$) administered on day 4 or day 8, respectively (Ghanayem et al. 1992). Three untreated rats received the same dose of [^{14}C]2-butoxyethanol(40-50 $\mu\text{Ci/kg}$). Tissue disposition and urine analyses of 2-butoxyethanol metabolites were performed. No quantitative or qualitative alterations of 2-butoxyethanol metabolism or its disposition were caused by repeated exposure to 2-butoxyethanol as compared to treatment with a single dose. The ratios of free 2-butoxyacetic acid, the 2-butoxyethanol-glucuronide and 2-butoxyethanol-sulfate conjugates, and parent 2-butoxyethanol excreted in the urine of rats treated for 4 or 8 days were relatively similar to those from rats treated with a single dose.

Male Fischer 344/N rats were allowed access for 24 hours to uniformly labeled [^{14}C]2-butoxyethanol in drinking water at three doses (Medinsky et al. 1990). Elimination of radioactivity was monitored for 72 hours. The labeled 2-butoxyethanol was administered at doses of 290, 860, or 2,590 ppm in drinking water, resulting in consumption of 237, 401, or 1,190 $\mu\text{mol/kg/body weight}$ (28, 47, or 141 mg/kg/day). The majority of the ^{14}C was excreted in urine, with 50-60% of the dose as free 2-butoxyacetic acid, or exhaled as CO_2 (8-10% of the dose); less than 5% of the dose was exhaled as unmetabolized 2-butoxyethanol. Ethylene glycol was excreted in urine, representing approximately 10% of the dose of 2-butoxyethanol. Unmetabolized 2-butoxyethanol and its glucuronide conjugate were also identified in the urine of animals dosed with 2-butoxyethanol.

A metabolism study was conducted to assist in validation of a PBPK model for 2-butoxyethanol kinetics (Corley et al. 1994). Two groups of male Fischer 344 rats with indwelling jugular cannulae received radiolabeled 2-butoxyethanol at doses of 8.6 and 126 mg/kg by gavage in water. Animals were immediately placed in metabolism cages for collection of urine, feces, and CO_2 . Samples of blood were taken from each rat at 1, 3, 6, 12, and 24 hours postdosing for determination of 2-butoxyethanol and free 2-butoxyacetic acid. Urine was collected at intervals of 0-12 and 12-24 hours postdosing. Urine samples were analyzed for total radioactivity and metabolite profile. The overall disposition of 2-butoxyethanol in this study was similar to that reported by Ghanayem et al. (1987c). At the low dose, approximately 59% of the dose was excreted in the urine during the first 24 hours, and 7.2% was excreted as CO_2 . At 126 mg/kg, 38-70% of the dose was

2. HEALTH EFFECTS

eliminated in the urine, and 8% was eliminated as CO₂. Metabolite profiles in the urine were similar to those reported by Ghanayem et al. (1987c) and Medinsky et al. (1990), and indicated that nearly 40% of the radioactivity in the urine was present as free 2-butoxyacetic acid during the first 12 hours following administration of 8.6 mg/kg, and nearly 65% after 126 mg/kg. An additional 15% of the radioactivity in the urine was present as the glucuronide conjugate of 2-butoxyethanol at the lower dose, and 10% was present at the higher dose. There was no evidence of further conjugation of 2-butoxyacetic acid under the enzyme/hydrolysis conditions used in this study. Ethylene glycol was present in smaller quantities (2-11% of the total radioactivity). An explanation of the analytic preparation is provided in Chapter 6.

The metabolism of 2-butoxyethanol following 6-hour nose-only inhalation exposure of male Fischer 344 rats was determined at different inhaled concentrations (Sabourin et al. 1992a). The uptake and metabolism of 2-butoxyethanol were essentially linear up to 438 ppm. From 17% to 24% of the inhaled compound was metabolized. Most (64-76%) of the inhaled [¹⁴C]2-butoxyethanol was eliminated in the urine, with free 2-butoxyacetic acid being the major urinary metabolite (37-43%), accompanied by lesser amounts of ethylene glycol (8-16%) and 2-butoxyethanol glucuronide (3-10%). A small proportion (5-8%) of the retained 2-butoxyethanol was exhaled as ¹⁴CO₂. Most (>80%) of the [¹⁴C]2-butoxyethanol-derived material in blood was in the plasma. Free 2-butoxyacetic acid was the major metabolite of 2-butoxyethanol in plasma. Ratios of ethylene glycol to 2-butoxyacetic acid in plasma were higher than those in urine. Urinary metabolites were monitored at various times up to 66 hours postexposure. More than 88% of the total radioactivity excreted was excreted during the first 41 hours. Free 2-butoxyacetic acid was the major metabolite in the urine at all exposure concentrations; ethylene glycol and 2-butoxyethanol glucuronide were also found in lesser amounts. As the exposure concentration increased, the proportion of two unidentified minor metabolites increased, and the time required for urinary excretion of [¹⁴C]2-butoxyethanol equivalents also increased. At 49 ppm, metabolism to the glucuronide was favored during exposure, whereas metabolism to free 2-butoxyacetic acid and ethylene glycol was favored at later times postexposure. The pattern was even more apparent at the higher dose. CO₂ production most closely followed ethylene glycol production. The study authors suggested that these results indicate that, in rats, overall metabolism of 2-butoxyethanol to 2-butoxyacetic acid, the hemolytic metabolite, was linearly related to the exposure concentration up to a concentration that caused severe toxicity (438 ppm). Assuming that the toxicity of inhaled 2-butoxyethanol is directly proportional to the formation of 2-butoxyacetic acid, the authors suggested that the toxicity of inhaled 2-butoxyethanol can be expected to be linearly related to the exposure concentration up to exposure concentrations that cause mortality.

2. HEALTH EFFECTS

Three different amounts of [^{14}C]2-butoxyethanol (61, 181, and 288 mg/kg) were applied to same-sized areas on the clipped backs of Fischer 344/N rats, and nonoccluded percutaneous absorption was measured (Sabourin et al. 1992b, 1993). The rates of excretion by different routes of the ^{14}C -labeled parent compound and metabolites were measured, as well as the amount of ^{14}C remaining in the carcass. Within the dose range studied, the absorption and metabolism of 2-butoxyethanol by Fischer 344/N rats were linearly related to the dermally applied dose. Free 2-butoxyacetic acid was the major metabolite. The 2-butoxyethanol-glucuronide was also detected in the urine. The formation of small amounts of ethylene glycol indicated cleavage of the ether bond. Plasma metabolites were evaluated at the mid-dose, in which no significant hemolysis was detected. Over 80% of the blood radioactivity was associated with the plasma and less than 20% was associated with the red blood cells. The concentration of total plasma metabolites was nine times higher than that of the parent compound, 2-butoxyethanol, in the plasma. Peak levels of radioactivity were reached at about 1 hour, with a half-life of about 4 hours. Free 2-butoxyacetic acid was the major metabolite and represented 53-75% of the plasma radioactivity.

Comparison of the profiles of urinary metabolites from inhalation, oral, and dermal exposure of rats to 2-butoxyethanol at low, middle, and high doses suggests that the route of administration influences the relative amount of metabolites (Medinsky et al. 1990; Sabourin et al. 1992a, 1992b, 1993; Shyr et al. 1993). In all exposure routes, free 2-butoxyacetic acid is the major metabolite of 2-butoxyethanol, but the relative proportions of minor metabolites can be influenced by route of exposure. Exposure by oral (drinking water) or inhalation routes generally favors production of ethylene glycol as compared to the glucuronide, with the exception of low-level drinking water exposure and the high-dose inhalation exposure, after which the amounts of the two metabolites were not statistically different. Dermal exposure favors production of the 2-butoxyethanol-glucuronide, possibly because of the more rapid administration of 2-butoxyethanol by this route, which in turn saturates the metabolic pathway and shift metabolism to 2-butoxyethanol-glucuronide conjugation.

The metabolism of 2-butoxyethanol (^{14}C -labeled at both ethanol carbons) by human and rat hepatocytes has been studied *in vitro* (Green et al. 1996). Following a 4-hour incubation period, rat hepatocytes produced more ethylene glycol and more free 2-butoxyacetic acid at all concentrations tested (0.02, 0.2, 2, and 10 mM). As indicated in Table 2-8, there was evidence of saturation of the ethylene glycol pathway in both species at 0.2 mM, and of the 2-butoxyacetic acid pathway in rats at 10 mM, and in humans at 2 mM. The glucuronide conjugate of 2-butoxyethanol was tentatively identified in the incubation media of both species. Kinetic parameters, calculated using Eadie-Hofsee plots, were maximum velocity (V_{\max}) of 113 ± 58 and

Table 2-8. Metabolism of 2-Butoxyethanol by Human and Rat Hepatocytes *In Vitro*^{a,b}

Concentration (mM)	Human hepatocytes % of total radioactivity as:			Rat hepatocytes % of total radioactivity as:		
	2-Butoxyethanol ^c	2-Butoxyacetic ^d acid	Ethylene glycol	2-Butoxyethanol ^c	2-Butoxyacetic ^d acid	Ethylene glycol
0.02	40.8±19.1	51.8±18.6	4.4±1.9	<0.4	77.3±0.4	8.6±1.5
0.2	54.7±18.6	42.2±18.5	3.1±1.8	0.3±0.5	91.5±1.4	5.9±1.0
2	83.3±8.5	14.5±8.3	1.6±0.9	7.5±9.3	82.6±6.1	4.2±1.2
10	93.1±2.0	4.6±1.1	1.5±0.8	66.1±8.0	28.2±3.8	2.6±1.3

^aValues are the amounts detected after 4 hours of incubation and are the mean and standard deviation of four experiments for humans and three experiments for rats.

^bDerived from Green et al. (1996).

^cValues include the glucuronide conjugate of 2-butoxyethanol.

^dValues are free 2-butoxyacetic acid.

2. HEALTH EFFECTS

74 1 ± 265 nmol/hour/ 10^6 hepatocytes for humans and rats, respectively, and metabolism rate constants (K_m) of 0.9 ± 0.3 and 0.9 ± 0.5 mM for humans and rats, respectively.

The metabolism of 2-butoxyethanol acetate has not been extensively studied, presumably because 2-butoxy-ethanol acetate is assumed to be metabolized to 2-butoxyethanol in the body, and then to follow the same pathway as 2-butoxyethanol, since 2-butoxyacetic acid has been detected in human urine after 2-butoxyethanol acetate exposure (Johanson et al. 1989).

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Elimination and excretion of 2-butoxyethanol after inhalation exposure appears to be similar in both humans and animals. Human studies suggest that excretion of 2-butoxyacetic acid is variable. Volunteers were exposed to 98 or 195 ppm 2-butoxyethanol for 8 hours (Carpenter et al. 1956). Urinalyses for free 2-butoxyacetic acid were conducted on urine samples collected during the 24 hours following the end of the exposure period. Results showed that at the 195-ppm exposure level, one male excreted 175 mg and one female excreted 300 mg of 2-butoxyacetic acid in the 24-hour period. Another male exposed to 195 ppm excreted only trace amounts of 2-butoxyacetic acid. Subjects exposed to 98 ppm ($n=4$) showed the following values for excreted 2-butoxyacetic acid: 100 mg (one female), 183 mg (one female), 75 mg (one male), 250 mg (one male). Since a substantial fraction of butoxyacetic acid can be excreted in the urine as the amino acid conjugate, some of the observed variability could come from the proportion conjugated.

Seven male volunteers were exposed to 2-butoxyethanol for 2 hours at the Swedish occupational exposure limit (20 ppm or 0.85 mmol/ m^3) during light physical exercise on a bicycle ergometer (Johanson et al. 1986a). Expired air was collected at regular time intervals for estimation of the respiratory uptake of the solvent. Capillary blood and urine were sampled, during and after the exposure period, and analyzed for 2-butoxyethanol and its metabolite, free 2-butoxyacetic acid. 2-Butoxyethanol was no longer detectable in the blood 2-4 hours after the end of exposure. The apparent values of elimination half-time, mean residence time, total blood clearance, and steady-state volume of distribution were 40 minutes, 42 minutes, 1.2 L/minute, and 54 L, respectively, for 2-butoxyethanol. The half-life for 2-butoxyethanol in urine was 1.36 hours. The amount of 2-butoxyethanol excreted in urine was less than 0.03% of the total uptake, while that of 2-butoxyacetic acid ranged from 15% to 55%. The excretion rate of free 2-butoxyacetic acid in urine

2. HEALTH EFFECTS

as well as the concentration varied more than 10-fold among subjects. There were increases in the concentration and excretion rate during the first few hours, with maximums reached after 5-12 and 2-10 hours, respectively. The half-life of 2-butoxyacetic acid in urine was 5.77 hours. The total urinary excretion averaged 496 μmol . Relative to the uptake of 2-butoxyethanol, the excretion averaged 41% on an equimolar basis.

Venous blood samples were collected from five healthy male volunteers prior to and after inhalation exposure to 20 ppm 2-butoxyethanol (the Swedish permissible exposure limit) during light physical exercise for 2 hours (Johanson and Johnsson 1991). The low renal clearance of free 2-butoxyacetic acid (22-39 mL/minute) compared with the average glomerular filtration rate of about 125 mL/minute indicates extensive binding to blood proteins and poor tubular secretion of the substance. Binding of 2-butoxyacetic acid to blood components is also indicated by the low apparent volume of distribution of approximately 15 L, which is about the volume of the extracellular water compartment. The study authors applied a one-compartment model for the kinetics of 2-butoxyacetic acid in blood with an average half-life of 4.3 hours, extrapolated to 1 workday (8 hours) of continuous exposure, and predicted a blood level of 114 μmol (15.1 mg/L) and a steady-state of 157 μmol (20.7 mg/L). The authors suggested that if dermal contact is avoided, inhalation exposure to 20 ppm 2-butoxyethanol, even for extended periods of time, is unlikely to cause adverse effects in humans.

Individual exposure to 2-butoxyethanol acetate was measured by personal air sampling (air samples collected from the breathing zone of workers and samples analyzed by gas chromatography) and biological monitoring of urine from 19 employees in an 8-hour work day in four silk-screen printing installations (Johanson et al. 1989). The samples were analyzed by gas chromatography. Urine was quantitatively collected from each subject two or three times during the day. Free 2-butoxyacetic acid could be detected in the low FM range in the personal air samples and in the urine. 2-Butoxyethanol acetate was detected in the personal air samples of five individuals, with an average concentration of 0.44 ppm. The detection limit was 0.015 ppm in air. Free 2-butoxyacetic acid was detected in the urine of 12 individuals, at an average concentration of 8 μM (0.132 mg/L).

Studies have addressed the issue of excretion of conjugated forms of 2-butoxyacetic acid in the urine of exposed individuals (Rettenmeier et al. 1993; Sakai et al. 1994). In the study by Rettenmeier et al. (1993), urine samples (end of shift on Friday and prior to shift on the following Monday) were taken from six lacquer workers who used a 2-butoxyethanol-containing detergent to clean car body parts. Samples from the end of

2. HEALTH EFFECTS

shift on Friday contained relatively large amounts of both 2-butoxyacetic acid and its glutamine conjugate, whereas only trace amounts of these metabolites were detectable in the Monday samples. The end of shift Friday urinary concentrations of 2-butoxyacetic acid averaged 1.49 mmol/L (range: 0.13-5.91 mmol/L), and the urinary concentrations of the glutamine conjugate averaged 0.82 mmol/L (range: 0.12-2.45 mmol/L). The fraction of 2-butoxyacetic acid that was excreted in the urine as the amino acid conjugate, *N*-butoxyacetylglutamine, averaged 48% (16-64%) of the total 2-butoxyacetic acid excreted. Thus, the urinary excretion of 2-butoxyacetic acid (up to 45-fold) and the glutamine conjugate (up to 20-fold) varied widely in the six subjects, even though their exposure conditions were similar. In a similar study, Sakai et al. (1994) compared 2-butoxyacetic acid levels in the urine of workers exposed to 2-butoxyethanol, both with and without acid hydrolysis to convert conjugated metabolites to free 2-butoxyacetic acid. Conjugated metabolites accounted for 71% (44-92%) of the total 2-butoxyacetic acid found in the urine over a Monday through Friday work week. Sakai et al. (1994) attributed the differences in their data compared with the findings of Rettenmeier et al. (1993) to differences in the derivatization methods and the possible differences in the 2-butoxyethanol exposure concentrations. Furthermore, Sakai et al. (1994) found that the fraction excreted as the conjugate during the first 2 days of the work week was greater than the amount excreted during the remainder of the work week, indicating a gradual depression of metabolic capacity of 2-butoxyacetic acid conjugation over subsequent work days. Variability in the rate of conjugate formation probably accounts for the large variation in excretion of free 2-butoxyacetic acid observed in earlier studies of persons exposed to 2-butoxyethanol. In order to determine the amount of total 2-butoxyacetic acid, it is necessary to measure both free butoxyacetic acid as well as the conjugate form. An explanation of analytic preparation is provided in Chapter 6.

Animal studies indicate that 2-butoxyacetic acid, the urinary metabolite found in humans, is also found in laboratory animals after inhalation exposure (Carpenter et al. 1956; Ghanayem et al. 1987a; Jijnsson and Steen 1978; Sabourin et al. 1992a). Twenty-seven female rats were exposed to 400 ppm (~561 mg/d), 17 female rats to 200 ppm (~281 mg/d), and 12 female rats to 100 ppm (~140 mg/d) 2-butoxyethanol (Carpenter et al. 1956). The estimated amount of metabolite (free 2-butoxyacetic acid) excreted was calculated from the urine samples collected during the 24-hour exposure period. The estimated amounts of free 2-butoxyacetic acid excreted were as follows (mean value per animal): 14 mg from rats exposed to 400 ppm, 7 mg from rats exposed to 200 ppm, and 1 mg from rats exposed to 100 ppm. Concurrent studies showed that most of the metabolite was excreted within 24 hours. In the same experiment, guinea pigs exposed to 100 ppm (~194 mg/d) or 200 ppm (~387 mg/d) 2-butoxyethanol excreted 4-5 mg in 24 hours, dogs exposed to 200 (~4,162 mg/d) and 400 ppm (~8,325 mg/d) excreted 42-100 mg, and rabbits exposed

2. HEALTH EFFECTS

to 200 ppm (~1,936 mg/d) and 400 ppm (~3,872 mg/d) excreted 12-23 mg and 89-302 mg, respectively. A correlation between vapor concentration and excretion of 2-butoxyacetic acid was observed for all animals tested except dogs. Additional studies of monkeys and dogs exposed to doses of 100-385 ppm 2-butoxyethanol for 28-90 days were also conducted, but the information was scanty and did not serve to clarify relative excretion rate by different species (Carpenter et al. 1956). The excretion of 2-butoxyethanol following 6-hour nose-only inhalation exposure of male Fischer 344 rats was determined at different inhaled concentrations (Sabourin et al. 1992a). The majority of the inhaled [¹⁴C]2-butoxyethanol was eliminated in the urine, with free 2-butoxyacetic acid being the major urinary metabolite, accompanied by lesser amounts of ethylene glycol and 2-butoxyethanol glucuronide. A small proportion (5-8%) of the retained 2-butoxyethanol was exhaled as ¹⁴CO₂. Ratios of ethylene glycol to 2-butoxyacetic acid in plasma were higher than those in urine. Feces accounted for 1-2% of the absorbed dose, whereas the carcass contained 13-20%. After exposure, 2-5% of the absorbed 2-butoxyethanol was exhaled unchanged. Urinary metabolites were monitored at various times up to 66 hours postexposure. More than 88% of the total radioactivity excreted was excreted during the first 41 hours. Free 2-butoxyacetic acid was the major metabolite in the urine at all exposure concentrations. Ethylene glycol and 2-butoxyethanol glucuronide were also found in lesser amounts. As the exposure concentration increased, the proportion of two unidentified minor metabolites increased. As the exposure concentration increased, the time required for urinary excretion of [¹⁴C]2-butoxyethanol equivalents also increased. At 4.3 ppm, about 60% of the urinary radioactivity was excreted during the 6-hour exposure, whereas at 438 ppm, only 10% was excreted during the exposure period. At 49 ppm, metabolism to the glucuronide was favored during exposure, whereas metabolism to free 2-butoxyacetic acid and ethylene glycol was favored at later times postexposure. The pattern was even more apparent at the higher dose. CO₂ production most closely followed ethylene glycol production and may represent the breakdown of this metabolite.

Experiments designed to determine the effect of age on the toxicity and metabolism of 2-butoxyethanol indicate that in rats, young animals (4-5 weeks old) are more resistant to the toxic effects than are older rats (9-13 weeks old) receiving an equivalent dose (Ghanayem et al. 1987a). A significantly higher percentage of the administered dose was exhaled as CO₂ in young rats compared to adult rats (22% versus 10%). Young rats excreted a higher percentage of the dose in the urine compared to adult rats (60% versus 40%). Young rats excrete less free 2-butoxyacetic acid than adult rats, and more 2-butoxyethanol-glucuronide; and no sulfate conjugate of 2-butoxyethanol was detected. High-performance liquid chromatography analysis of the urinary metabolites of 2-butoxyethanol in adult and young rats showed that the ratio of free 2-butoxyacetic acid to the total amount of the glucuronide and sulfate conjugates of 2-butoxyethanol (previously thought to

2. HEALTH EFFECTS

reflect an activation/detoxification index of 2-butoxyethanol) was significantly higher in older rats. An unknown metabolite was found in the urine of both young and adult rats at 6-8% and 1%, respectively.

In a more recent study, eight male Sprague-Dawley rats were exposed to 20 or 100 ppm 2-butoxyethanol 24 hours per day for 1, 2, 3, 4, 6, 8, 10, or 12 days (Johanson 1994). Urine was collected at 24-hour intervals. At the end of the exposure period, animals were killed and blood, muscle, liver, and testes samples were collected. Blood and tissue samples were analyzed for free 2-butoxyethanol and free 2-butoxyacetic acid by electron capture gas chromatography. No control group was used. Total blood clearance values were 2.3 L/hour/kg for the 20-ppm group and 2.2 L/hour/kg for the 100-ppm group, and rates were not significantly different. The urinary excretion rate for 2-butoxyacetic acid in the 20-ppm group averaged 0.20 mmol/day, whereas the 100-ppm group excreted 1.03 mmol/day. The observed urinary excretion rate corresponded to 64% of the calculated respiratory uptake and renal clearance of 0.53 L/hour for both groups.

2.3.4.2 Oral Exposure

A case report of a woman admitted to the hospital after ingestion in a suicide attempt of 250-500 mL of a window-cleaner containing 12% (467-933 mg/kg) 2-butoxyethanol, indicated that metabolic acidosis, hypokalemia, a rise in serum creatinine level, and a markedly increased urinary excretion of oxalate crystals were observed, suggesting a metabolic pattern after absorption from the stomach (Rambourg-Schepens et al. 1988). Kinetic evaluation of urinary excretion of 2-butoxyethanol, free 2-butoxyacetic acid, and oxalate indicated that 2-butoxyethanol was at the highest level of excretion at 1 day after ingestion (2-3 g/g creatinine). 2-Butoxyacetic acid peaked between the 2nd and 3rd days of ingestion at 40 g/g creatinine and was not detectable on day 8. Oxalate excretion was biphasic, reaching similar peak levels of approximately 40 g/g creatinine on day 1 and day 7 after ingestion. The high output of the oxalate in the urine was explained by the metabolism of 2-butoxyethanol to ethylene glycol which is further metabolized to oxalic acid. The biphasic aspect of the oxalate excretion was not specifically addressed by the study authors, but since the two pathways of metabolism (to 2-butoxyacetic acid and ethylene glycol-oxalic acid) occur simultaneously, the biphasic response may be the result of competition for the pathways. This assumption was supported by the existence of metabolic acidosis contemporary with the urinary peak oxalate level. Similar metabolic effects have been reported by others (Bauer et al. 1992; Gijsenbergh et al. 1989).

A 23-year-old woman weighing 64 kg was admitted to the hospital approximately 1 hour after ingesting 500 mL window-cleaner containing 2-butoxyethanol(391-469 mg/kg) and ethanol (Gijsenbergh et al. 1989).

2. HEALTH EFFECTS

The half-lives of ethanol (from the cleaning fluid) and 2-butoxyethanol in the blood were 20 and 210 minutes, respectively. The half-life of 2-butoxyethanol was longer than expected, perhaps because of saturation of metabolism and competitive inhibition by ethanol. 2-Butoxyacetic acid was highest in the dialysis fluid (738 mg/L) at the initiation of dialysis and decreased thereafter. A concomitant increase in 2-butoxyacetic acid in the urine was seen with the initiation of dialysis, and concentrations reached a peak of approximately 8 g/g creatinine 1.3 hours after the start of dialysis. The half-life of free 2-butoxyacetic acid in the urine after the start of dialysis was 5.3 hours.

Studies in animals indicate that 2-butoxyethanol is excreted through the urine, lungs, feces, and bile after exposure (Ghanayem et al. 1987b, 1987c). Male Fischer 344 rats were given single oral doses of [¹⁴C]2-butoxyethanol of 125 or 500 mg/kg. Rats were placed in metabolism cages and monitored for 48 hours after treatment. Expired air, urine, and feces were collected and monitored for ¹⁴C-associated radioactivity. Bile was collected from the common bile duct. The major route of elimination was the urine (40-70%), followed by exhalation (~18%). A small portion was excreted in the bile (8% at the 500-mg/kg dose) 8 hours after dosing, and a small amount was detected in the feces (2-3%).

Ghanayem et al. (1992) studied the differences in elimination of single or multiple oral doses of 2-butoxyethanol administered to rats, and found no quantitative or qualitative alterations of metabolism or disposition caused by repeated exposure to 2-butoxyethanol as compared to treatment with a single dose. Elimination of ¹⁴CO₂ and 2-butoxyethanol-derived radioactivity in the urine of rats receiving multiple doses of 2-butoxyethanol was essentially the same as for rats receiving a single dose. The ratios of free 2-butoxyacetic acid, the 2-butoxyethanol-glucuronide and 2-butoxyethanol-sulfate conjugates, and parent 2-butoxyethanol excreted in the urine of rats treated for 4 or 8 days were relatively similar to those from rats treated with a single dose.

Male Fischer 344/N rats were allowed access for 24 hours to uniformly labeled [¹⁴C]2-butoxyethanol in drinking water at three doses (Medinsky et al. 1990). Elimination of radioactivity was monitored for 72 hours. 2-Butoxyethanol was administered at doses of 290, 860, or 2,590 ppm in drinking water, resulting in consumption of 237, 401, or 1,190 μmol/kg/day (28, 47, or 141 mg/kg/day). The majority of the ¹⁴C was excreted in urine as free 2-butoxyacetic acid (50-60% of the dose), or exhaled as CO₂ (8-10% of the dose). Less than 5% of the dose was exhaled as unmetabolized 2-butoxyethanol. Ethylene glycol was excreted in urine, representing approximately 10% of the dose of 2-butoxyethanol. Elimination in the feces was a minor pathway for 2-butoxyethanol (1.6-2.8% of the dose). Unmetabolized 2-butoxyethanol and its glucuronide conjugate were also identified in the urine of animals dosed with 2-butoxyethanol. The time course for

2. HEALTH EFFECTS

excretion of 2-butoxyethanol metabolites during and after exposure to the lowest dose indicated that the maximum excretion occurs during the first 12-24 hours after the start of exposure. This time course corresponds to the active period (nocturnal) for these animals, and the period during which they are likely to drink the most water. No evidence of the glycine conjugate of 2-butoxyacetic acid was found. The amount of ^{14}C -derived radioactivity found in the carcasses of animals ranged from 3 to 23.7 μmoles (2.8-9.8% of the dose) for the low- to high-dose groups.

2.3.4.3 Dermal Exposure

Worker exposures to 2-butoxyethanol were evaluated by environmental and biological monitoring for 29 employees in five shops where window-cleaning agents had been used (Vincent et al. 1993). Each of the 29 employees was exposed to 2-butoxyethanol. Eleven men and two women were involved in cleaning cars in four garages. The remaining 16 were office cleaners. Only two of the workers who cleaned new cars wore protective gloves. The study authors suggested that the primary route of exposure was dermal, although some inhalation exposure necessarily occurred. Each of the window-cleaning agents sampled contained 2-butoxyethanol in concentrations ranging from 0.9% to 21.2% in volume. Window-cleaner use times ranged from 120 to 320 minutes per day, and quantities of cleaning agents ranged from 220 to 1,200 mL/day for individuals involved in cleaning new cars. The corresponding figures for cleaners of used cars were 20-50 minutes and 50-100 mL. For office cleaners, the corresponding figures were 15 minutes per day and <50 mL, of cleaning agent used per day. For cleaners of new cars, the mean 2-butoxyethanol exposure was 2.33 ppm (range: <0.10-7.33 ppm), and the mean urinary free 2-butoxyacetic acid concentration in endshift samples was 111.3 mg/g creatinine (range: 12.7-371 mg/g creatinine). The mean preshift (average of Monday and Friday) urinary free 2-butoxyacetic acid concentration was 17.9 mg/g creatinine (range: 2-98.6 mg/g creatinine). For cleaners of used cars, the mean 2-butoxyethanol exposure was 0.36 ppm (range: <0.10-1.52 ppm), and the mean urinary free 2-butoxyacetic acid concentration in endshift samples was 6.3 mg/g creatinine (range: 2-24.4 mg/g creatinine). The mean preshift urinary concentration of free 2-butoxyacetic acid was 4.8 mg/kg creatinine (range: 2-33 mg/g creatinine). For the office cleaners, the mean 2-butoxyethanol concentration was 0.32 ppm (range: <0.30-0.73 ppm), and the mean urinary free 2-butoxyacetic acid concentration in endshift samples was 2.1 mg/g creatinine (range: 2-4.6 mg/g creatinine). The mean preshift urinary concentration of free 2-butoxyacetic acid was 2.1 mg/g creatinine (range: 2-4.6 mg/g creatinine). Correlations of 2-butoxyethanol exposure in air and endshift concentrations of urinary free 2-butoxyacetic acid from cleaners of new and used cars (for which the data were most complete) indicated a log-linear relationship. From these results, the study authors estimated that exposure to

2. HEALTH EFFECTS

window cleaners containing 5.7-21.2% 2-butoxyethanol by volume for a period of 160 minutes would result in an endshift urinary concentration of free 2-butoxyacetic acid of 60 mg/g creatinine. A similar relationship was observed for urinary free 2-butoxyacetic acid concentrations and utilization time for office cleaners.

The percutaneous absorption of 2-butoxyethanol was investigated in 12 exposure experiments with five male volunteers. All were nonsmokers and stated low or no consumption of alcohol (Johanson et al. 1988). None had been exposed to industrial solvents. All had participated in a previous study of 2-butoxyethanol (Johanson et al. 1986a). The subjects kept two or four fingers immersed in neat 2-butoxyethanol for 2 hours. Urine was collected for 24 hours and analyzed for the metabolite free 2-butoxyacetic acid. The presence of 2-butoxyethanol in blood and of free 2-butoxyacetic acid in urine, detected by gas chromatography, confirmed that 2-butoxyethanol enters the systemic circulation in human males during even minimal dermal exposure. The half-life of 2-butoxyethanol during the decay phase ranged from 0.6 to 4.8 hours (geometric mean: 1.3 hours). The excretion rate of 2-butoxyacetic acid increased during the first hours after exposure, reached a maximum at about 5 hours (3 hours postexposure), and then declined, with an average half-life of 3.1 hours. Seventeen percent of the absorbed dose was excreted as 2-butoxyacetic acid in 24 hours. The cumulative excretion of free 2-butoxyacetic acid ranged from 8.7 to 313 μM (1.15-41.37 mg).

In six men exposed one-arm only to 50 ppm [$^{13}\text{C}_2$] 2-butoxyethanol for 2 hours, about two-thirds of the 2-butoxyacetic acid excreted in the urine was in the form of the N-butoxyacetyl glutamine conjugate (Corley et al. 1997). No free 2-butoxyethanol, free or conjugated ethylene glycol ether, or glycolic acid (a metabolite of ethylene glycol) were detected in the urine. 2-Butoxyacetic acid was eliminated in the urine primarily during the first 12-hour collection period.

In a study in male and female Wistar rats, [^{14}C]2-butoxyethanol was applied to the shaven skin on a 12- cm^2 area under a protective glass capsule at a dose of 200 mg/kg (Bartnik et al. 1987). Urine was collected at intervals of 0-8, 8-24, and 24-48 hours following application and stored at -80°C . Radioactivity of urine, cage rinse water, skin, and glass capsule was determined. Percutaneous absorption was assessed by using the measurements of urinary excretion of ^{14}C from 0 to 48 hours following cutaneous application of 2-butoxyethanol. Radioactivity in 48 hours following cutaneous application of radiolabeled 2-butoxyethanol showed that 20-23% of the applied dose was found in the urine, including cage rinse water, with no notable differences by sex. Over 95% of the radioactivity excreted in the urine was eliminated in 24 hours.

2. HEALTH EFFECTS

Three different amounts of the [^{14}C]2-butoxyethanol (61, 181, or 299 mg/kg) were applied to same-sized areas on the clipped backs of Fischer 344/N rats, and nonoccluded percutaneous absorption was measured (Sabourin et al. 1992b, 1993). The rates of excretion of the ^{14}C -labeled parent compound and metabolites were measured, as well as the amount of ^{14}C remaining in the carcass. The majority of the absorbed and metabolized glycol ether was excreted in the urine (82-83%); 3-5% was found as CO_2 , 3-6% was found in the feces, and 3-13% was found in the carcass. The percentage of glycol ether found tended to increase with increasing dose, although this was not consistently the case. Urinary metabolites were analyzed up to the time at which <10% of the excreted radioactivity. Urine was collected up to 23 hours postexposure. Free 2-butoxyacetic acid was the main metabolite (66-70%), followed by the 2-butoxyethanol-glucuronide (13-15%), and ethylene glycol(4-6%). CO_2 expired in the air was 3-4% in this experiment. The formation of small amounts of ethylene glycol indicated cleavage of the ether bond. Minor amounts of unidentified metabolites made up the remainder of the detected radioactivity.

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

2. HEALTH EFFECTS

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular chemical substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. This simplification, however, is desirable if the uptake and disposition of the chemical substance(s) is adequately described because data are often unavailable for many biological processes and using a simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance and thus the importance of model validation.

PBPK models improve the pharmacokinetic extrapolation aspects of the risk assessment process, which seeks to identify the maximal (i.e., safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based upon the results of studies where doses were higher or were administered in different species. Figure 2-7 shows a conceptualized representation of a PBPK model.

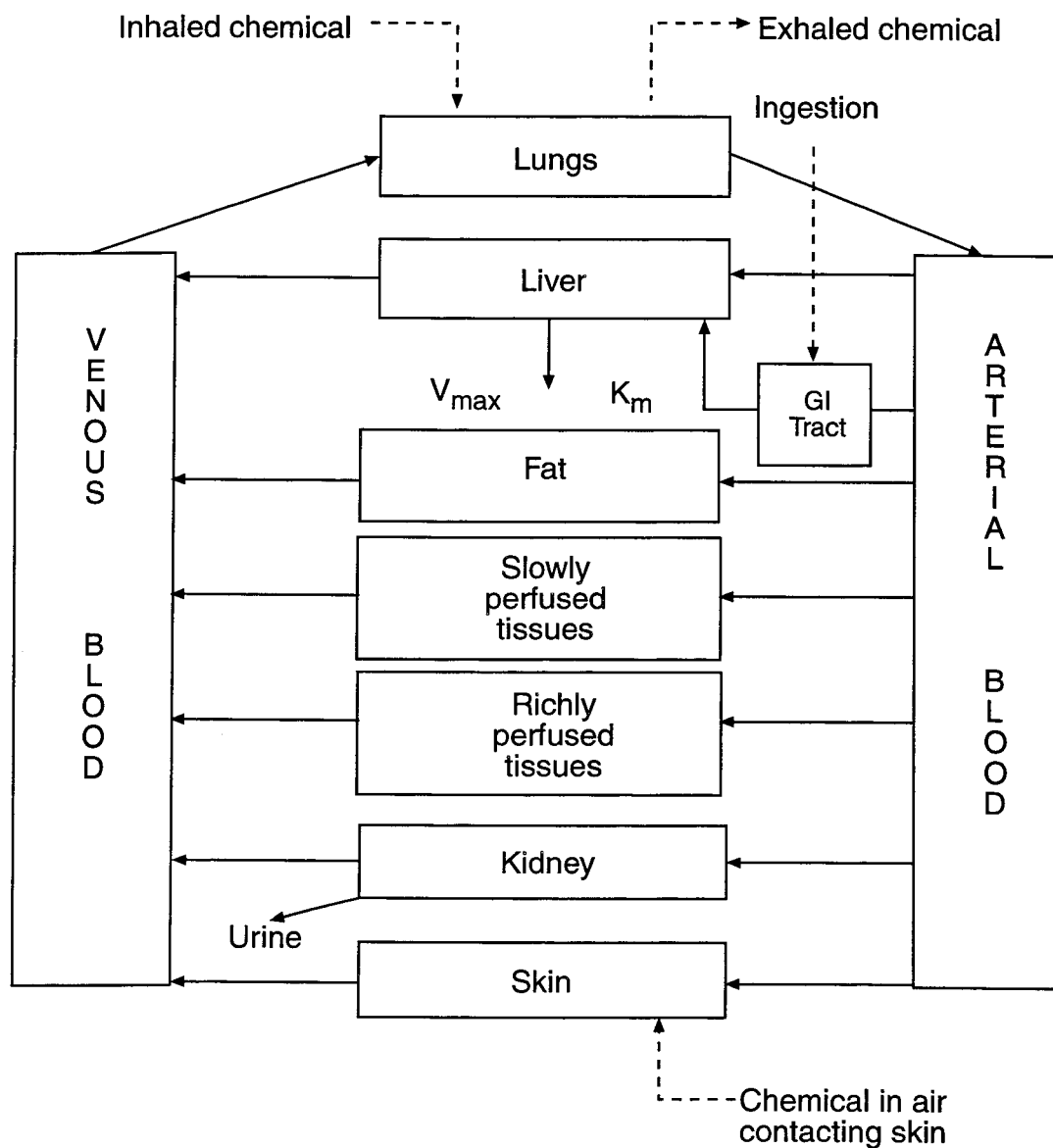
PBPK models for 2-butoxyethanol are discussed below. No specific models were found for 2-butoxyethanol acetate. However, it is expected that 2-butoxyethanol acetate follows a similar model after absorption and conversion to 2-butoxyethanol. However, the absorption of 2-butoxyacetic acid may be different from 2-butoxyethanol because of its different chemical form.

2.3.5.1 Summary of PBPK Models

PBPK models of 2-butoxyethanol absorption, metabolism, disposition, and excretion have been published by Johanson and coworkers (Johanson 1986,1991a; Johanson and Naslund 1988), Shyr et al. (1993), and Corley et al. (1994). They are presented in the order that they were published in the literature, since each

2. HEALTH EFFECTS

Figure 2-7. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

2. HEALTH EFFECTS

successive author used the data and results from the previous authors. Each successive model is more complete and more closely approaches modeling 2-butoxyethanol kinetics accurately. The Johanson model (Johanson 1986, 1991 a; Johanson and Naslund 1988) addressed human inhalation exposure to 2-butoxyethanol during rest and exercise, whereas the Shyr model (Shyr et al. 1993) addressed high-low dose and route of administration extrapolation based on animal data. The Corley model (Corley 1996; Corley et al. 1994) combined aspects of each of the other two models and also addressed 2-butoxyacetic acid disposition and competing metabolic pathways. Because no chronic data are available for either humans or animals, these models have not been validated for chronic exposure to 2-butoxyethanol.

2.3.5.2 2-Butoxyethanol PBPK Model Comparison

Three PBPK models that describe the disposition of 2-butoxyethanol have been identified from the open literature (late 1980s and forward). The first model (Figure 2-8) is based on human inhalation and perfused rat liver data, with later refinements (Johanson 1986, 1991a; Johanson and Naslund 1988). The second model (Figure 2-9) is based on rat data collected after inhalation, drinking water, and dermal exposure (Shyr et al. 1993). Shyr et al. (1993) also presented a model of the metabolic pathway of 2-butoxyethanol, as shown in Figure 2-10. The third model (Figure 2-11) was developed by Corley et al. (1994) and is an expansion of the Johanson model (Johanson 1986, 1991a; Johanson and Naslund 1988). It includes additional routes of exposure, physiological descriptions for rats, competing pathways for metabolism of 2-butoxyethanol, and measured partition coefficients for 2-butoxyethanol and 2-butoxyacetic acid. This model was further modified on the basis of data on human metabolites and dermal absorption of 2-butoxyethanol vapor (Corley et al. 1997).

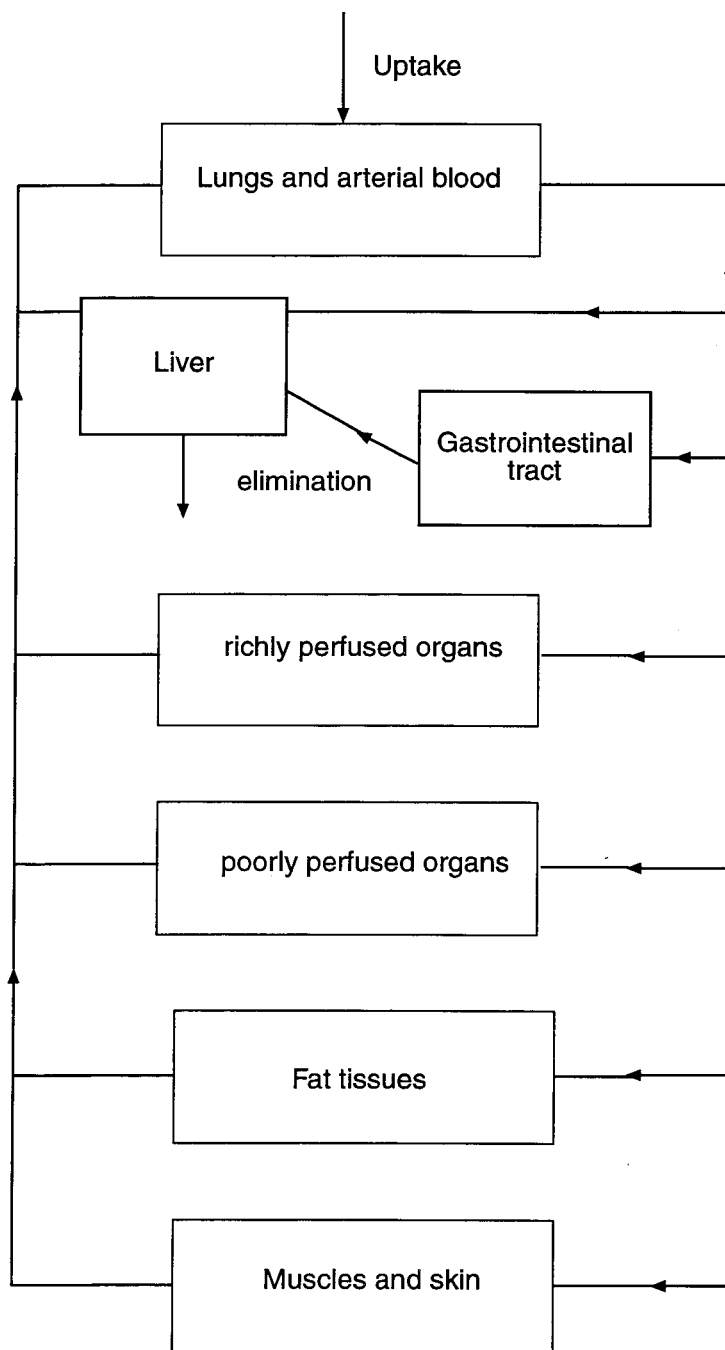
2.3.5.3 Discussion of Models

The Johanson Model

The Johanson model, with its refinements (Johanson 1986, 1991 a; Johanson and Naslund 1988), is one of the original PBPK models developed to describe and ultimately predict the effects of occupational inhalation exposure to 2-butoxyethanol and is depicted in Figure 2-8. Factors of exercise and co-exposure to ethanol are included.

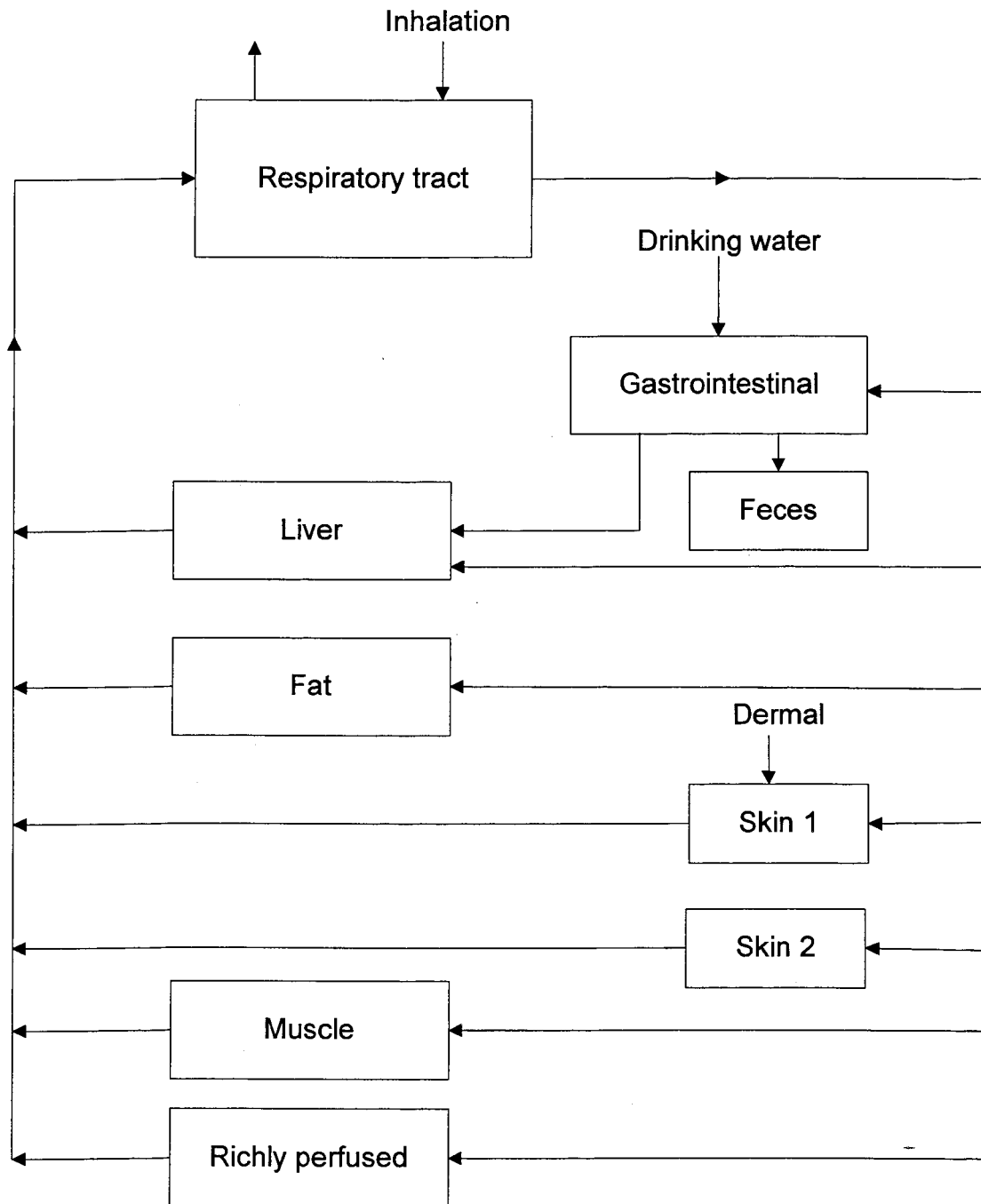
2. HEALTH EFFECTS

Figure 2-8. Schematic Drawing of PBPK Model for Simulation of 2-Butoxyethanol Toxicokinetics*



*Derived from Johanson 1986

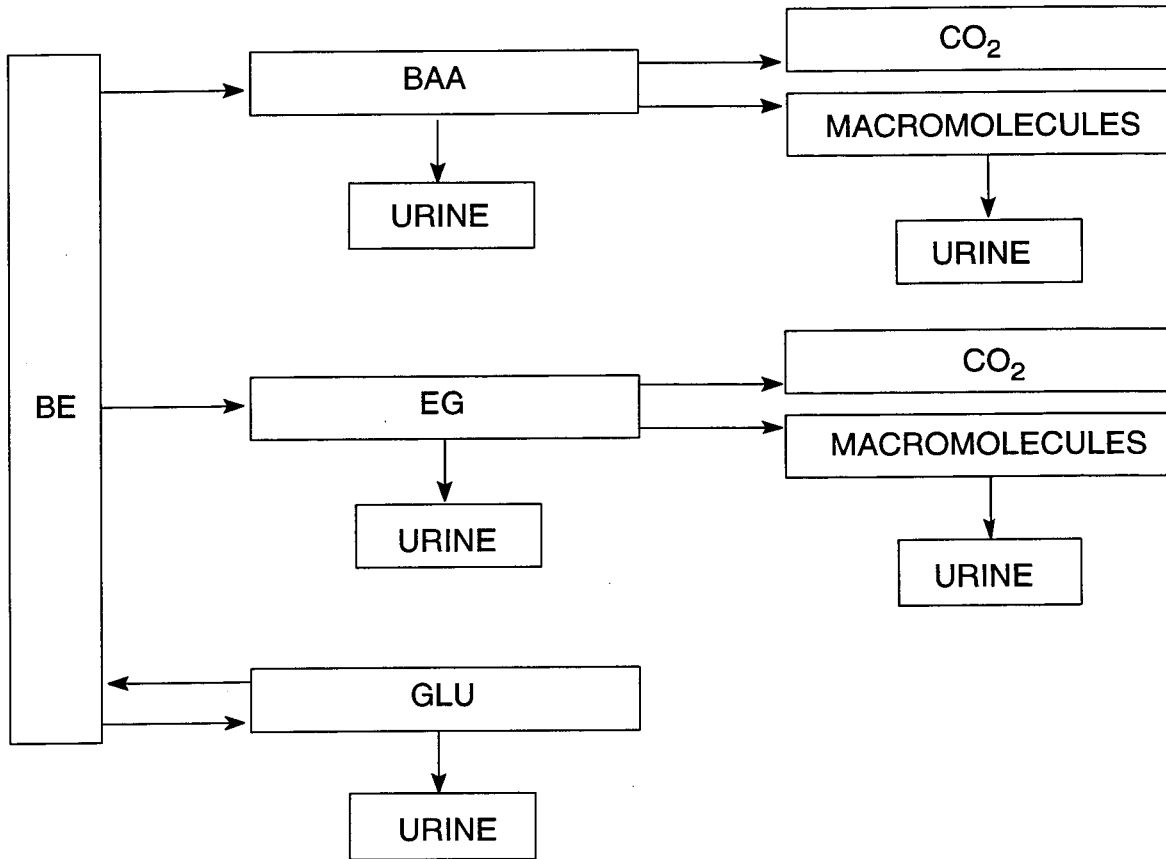
2. HEALTH EFFECTS

Figure 2-9. PBPK Model for 2-Butoxyethanol Disposition in Rats

Source: Shyr et al. 1993

Note: Skin 1 is the skin volume on which dermal dose was applied, and skin 2 is the rest of the skin volume.

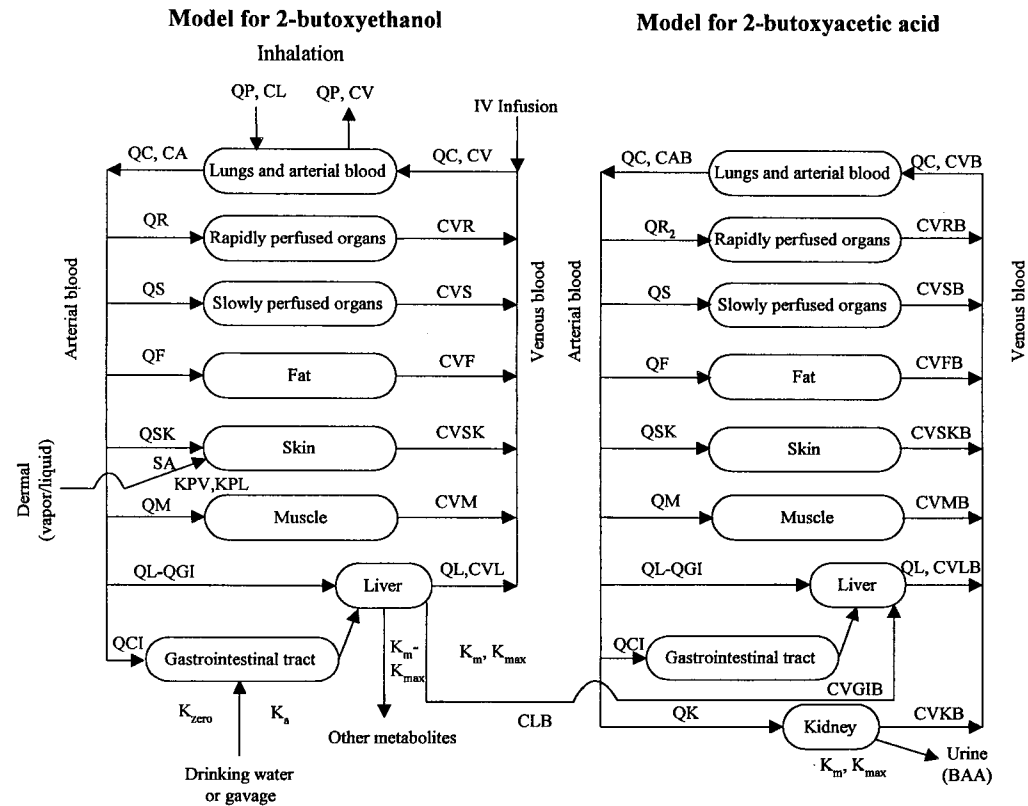
2. HEALTH EFFECTS

Figure 2-10. Model of Metabolic Pathway of 2-Butoxyethanol*

*Derived from Shyr et al. 1993

BAA = butoxyacetic acid; BE = 2-butoxyethanol; CO₂ = carbon dioxide; EG = ethylene glycol;
GLU = glucuronide;

Figure 2-11. PBPK Model of 2-Butoxyethanol and 2-Butoxyacetic Acid



Source: Corley et al. 1994

Note: Physiologically based pharmacokinetic model used to describe PBPK model of 2-butoxyethanol and 2-butoxyacetic acid. In rats and humans following inhalation (whole-body or nose/mouth only), oral (gavage and drinking water), intravenous infusion, and dermal (vapor and liquid) routes of exposure. CL, concentration of BE in inhaled air (mg/liter); CX, concentration of BE in exhaled air (mg/liter); QP, alveolar ventilation (liter/hr); QC, cardiac output (liter/hr); Q_i , blood flow to "i" tissue (liter/hr); CA, arterial blood concentration of BE (mg/liter); CAB, arterial blood concentration of BAA (mg/liter); CV, pooled venous blood concentration of BE (mg/liter); CV_i , venous blood concentration of BE draining "i" tissue (mg/liter); CVB, pooled venous blood concentration of BAA (mg/liter); CV_iB , venous blood concentration of BAA draining "i" tissue (mg/liter); SA, surface area of skin exposed (cm^2); KP, KPL, skin permeability coefficient for vapors or liquids, respectively (cm/hr); k_{zero} , zero-order rate of absorption of BE from water; k_a , first-order rate constant for absorption of BE from gavage dose (hr^{-1}); K_m , Michaelis constant for saturable process (mg/liter); V_{max} , maximum velocity for saturable process (mg/hr).

2. HEALTH EFFECTS

Risk assessment. This model successfully described the arterial blood concentrations of 2-butoxyethanol in a 70-kg man after inhalation exposure. Specifically, the model simulations indicated that for inhalation concentration of 20 ppm (the Swedish permissible exposure limit; U.S. limit = 25 ppm) for 2 hours accompanied by light physical exercise on an exercise bicycle, predicted arterial blood concentrations of 2-butoxyethanol agreed well with human experimental data (Johanson et al. 1986a). Simulations of inhalation exposure indicated that in humans, the concentration in blood increased in a linear manner throughout the 2-hour exposure, then declined rapidly to nearly non-detectable levels at 6 hours. By simulating different levels of physical activity at the same exposure level, but for 8 hours, mimicking a standard work day, Johanson's model was used to predict 2-butoxyethanol levels in blood after increased work load. As might be expected, the model predicts that with increased activity, and thus increased pulmonary blood flow and uptake of 2-butoxyethanol, arterial levels of 2-butoxyethanol increase proportionally during exposure, then decline rapidly after exposure ceases.

Simulations of co-exposure to ethanol (0.1% in the blood) during an 8-hour exposure to 20 ppm 2-butoxyethanol with no exercise predict that the arterial levels of 2-butoxyethanol will be elevated because of a decrease in elimination rate (Johanson 1986). Because the increase is due to decreased elimination and not increased uptake, the rise and fall of blood concentration of 2-butoxyethanol are slower in the ethanol co-administration model than in the increased workload model.

Description of the model. The Johanson 2-butoxyethanol PBPK model was designed to describe organic solvent kinetics in general. Certain limiting assumptions were made in the model. For instance, the organs are lumped into compartments according to blood flow and fat content (Johanson 1986). Muscles and skin form a separate compartment because of their wide variation in blood flow at different workloads. In the model, solvent uptake is assumed to occur only in the lung; elimination is assumed to occur in the liver. Instantaneous homogeneous distribution of the solvent in each compartment is assumed, and as a consequence, the solvent retained in the respiratory airways immediately reaches the arterial blood. A schematic representation of the Johanson model is shown in Figure 2-8, with only the inhalation route represented.

The tissue compartments included in the Johanson model are as follows: the lungs, presumed to be the only site of uptake, and arterial blood; the liver, presumed to be the only organ where transformation of 2-butoxyethanol takes place; the gastrointestinal tract in equilibrium with the liver; a group of richly perfused tissues; a group of poorly perfused tissues; a fat compartment; and muscles and skin. Support for the assumption

2. HEALTH EFFECTS

that the liver is the primary site of transformation of 2-butoxyethanol (as opposed to the kidney, for instance) comes from the investigator's observation that very little 2-butoxyethanol was recovered from the urine of men exposed to 2-butoxyethanol experimentally (Johanson et al. 1986a). All partition ratios between blood and other compartments were set to unity, based on preliminary studies on 2-butoxyethanol indicating a weak preference for water as compared to fat or protein. Diffusion equilibrium between end-capillary blood and tissue was assumed for all compartments.

Physiologic parameters used, biochemical constants, and partition coefficients in the model are shown in Table 2-9. Physiologic constants (organ volume, blood flows, etc.) and tissue and blood coefficients were taken from literature sources (Astrand 1983; Fiserova-Bergerova 1983a). Elimination constants for the liver were taken from experiments in the perfused rat liver (Johanson et al. 1986b). Venous equilibrium was assumed, and competitive inhibition between ethanol and 2-butoxyethanol was assumed.

Validation of the model. Since the model was developed using the data of Johanson et al. (1986a, 1986b), the model accurately reflects these data. Factors not taken into account in the model, but that may influence cardiac output and distribution and hepatic blood flow and thus, may have to be considered, include posture, thermal stress, food intake, pathological conditions, and the presence of other substances including drugs.

Target tissues. The model correctly described arterial blood concentrations of 2-butoxyethanol in human males during and after a 2-hour inhalation exposure to 20 ppm, accompanied by light physical exercise. Predictions of 2-butoxyethanol concentrations in muscle and skin may reflect blood sampled from peripheral veins, as would be accomplished in a biomonitoring program. The model shows that the rise and fall of 2-butoxyethanol in the arterial blood and lungs are faster than in the muscle and skin compartment. This suggests that venous blood sampling may be more useful than arterial sampling. A later refinement of the model included factors for "resting" and "working" skin and muscle, and data on tissueair partition coefficients were included, thus improving the predictive qualities of the model in an occupational setting (Johanson and Naslund 1988). Further refinement included modeling of the retention and excretion of solvent vapors in the various parts of the lung, including the trachea, main bronchi, lobar bronchi, segmental bronchi, subsegmental bronchi, small bronchi, bronchioles, terminal bronchioles, respiratory bronchioles, alveolar ducts, and alveoli, prior to equilibrating with other systemic compartments (Johanson 1991a). Data from 2-butoxyethanol experiments were included in the model (Johanson and Dynesius 1988; Johanson et al. 1986a).

2. HEALTH EFFECTS

Table 2-9. Parameters Used in the Johanson PBPK Model^{a, b, c}

Parameters ^{d, e}	Perfusion (L/Minute)				
	Volume (L)	Rest	Light exercise	Middle exercise	Strenuous exercise
Pulmonary ventilation		6.0	22.0	38.0	54
Lungs and arterial blood	2.0	5.1	10.1	14.1	16.6
Gastrointestinal tract	2.4	1.2	1.2	0.9	0.5
Liver	1.5	1.6	1.6	1.3	0.9
Richly perfused organs	2.1	2.1	2.7	2.7	2.8
Poorly perfused organs	12.5	0.1	0.1	0.1	0.1
Fat tissues	14.5	0.25	0.65	1.0	0.8
Muscles and skin	33.0	1.0	5.0	9.0	12.0

^aDerived from: Johanson 1986

^bVolumes and blood flows were calculated from data compiled by Astrand (1983) and Fiserora-Bergerova (1983a).

^cMetabolic constants were taken from *in vitro* experiments in perfused rat liver (Johanson et al. 1986b).

^dBody weight = 70.0 kg.

^eMetabolic and macromolecular binding constants: $V_{\max}C$ ($\mu\text{mol}/\text{minute}/\text{g liver}$) = 0.730; K_m (μM) = 228

2. HEALTH EFFECTS

The data clearly indicate that, for accurate biomonitoring, sampling should take place during exposure because of the rapid disappearance of 2-butoxyethanol from tissue compartments. Even in the compartment that shows the longest residence time (poorly perfused organs), practically no 2-butoxyethanol is present the morning following exposure. The model suggests that bioaccumulation does not generally occur, although accumulation by a particular organ (or in a disease state) could not be ruled out. The study authors state that human data, combined with the physicochemical properties of the chemical, do not suggest that specific organ binding would substantially alter the total body burden. The model does not address the kinetics of the major metabolite, 2-butoxyacetic acid.

Species extrapolation. The Johanson model uses human data to predict occupational exposure parameters. The author notes that the validity of the assumptions used to extrapolate to humans from *in vitro* hepatic elimination data on rats is not known.

High-low dose extrapolation. The model predicts nonlinearity due to saturated elimination at concentrations well above 100 ppm, even in combination with physical exercise and ethanol. The comparison between the simulated arterial blood levels and experimental arterial blood levels obtained after exposure to 20 ppm 2-butoxyethanol for 2 hours indicates linear kinetics at this concentration, which is lower than the PEL in the United States (PEL = 50 ppm, OSHA 1974). Thus, linear kinetics would be expected in ordinary occupational inhalation exposure, although low-dose extrapolation was not specifically addressed in this model.

Interroute extrapolation. The Johanson model was not used to predict the kinetic behavior of 2-butoxyethanol after dermal or oral exposure. The study author comments that saturation kinetics may occur after accidental or intentional ingestion of large amounts or after accidental dermal exposure to large volumes of 2-butoxyethanol, but not after exposure in a controlled occupational setting.

The Shyr Model

The Shyr model (Shyr et al. 1993) is based on experimental data from inhalation, drinking water, and dermal exposure experiments in rats (Figure 2-9). The major metabolite, 2-butoxyacetic acid, was included in the model in addition to the 2-butoxyethanol-glucuronide and ethylene glycol. A model formulation of the possible metabolic pathways based on experimental data was included (Figure 2-10).

2. HEALTH EFFECTS

Risk assessment. This model successfully described the differences in disposition of 2-butoxyethanol, based on urinary profiles of metabolites, in various exposure routes by taking into account the differences in absorption rate and by incorporating a minor pathway for metabolism (glucuronidation) by skin (Shyr et al. 1993). The model was reasonably successful in predicting the experimental rat data produced by Johanson et al. (1986a). The value of the model lies in the ability to extrapolate to the human situation from the routes of exposure likely to be used in experimental assays.

Description of the model. The Shyr 2-butoxyethanol PBPK model (Shyr et al. 1993) was based on an earlier PBPK model developed by Ramsey and Andersen (1984) to describe the disposition of styrene exposure in mice and rats, and on the Johanson (1986) model. A schematic representation of the Shyr model is shown in Figure 2-9, with inhalation, drinking water, and dermal routes represented. Parameters used in the model are summarized in Table 2-10.

The tissue compartments included in the Shyr model are as follows: respiratory tract; liver; gastrointestinal tract; fat; and a group of richly perfused tissues including kidney, bone marrow, and heart. Muscle and skin were separated into individual compartments to allow for the simulation of dermal exposure. The distribution of 2-butoxyethanol among compartments was assumed to be limited only by blood flow rate because the lipid solubility of 2-butoxyethanol allowed it to penetrate cell membranes rapidly. Liver was a major site of metabolism in the Shyr model with a minor amount of 2-butoxyethanol-glucuronide formed in the skin at the site of application for dermal exposure.

Drinking water exposure was simulated by estimating nocturnal drinking patterns of rats as a continuous activity. For dermal exposure, the rate of 2-butoxyethanol absorption through the skin was also estimated and adjusted according to the *in vitro* absorption data of Bartnik et al. (1987). A factor was included for dermal metabolism to the 2-butoxyethanol-glucuronide. Inhalation exposure was estimated using the model of Ramsey and Andersen (1984) with a factor for nasal absorption (Dahl et al. 1991). Nasal absorption includes dissolution of the compound in the nasal mucous membrane upon inhalation, and vaporization and elimination from the membranes into expired air. Based on the work of Dahl et al. (1991) in dogs, a high nasal uptake was assumed for compounds with high blood/air partitions. Increasing nasal absorption for soluble compounds is also suggested by Dahl et al. (1991). More recent work on kinetic models for respiratory uptake of inhaled volatiles has been done by Medinsky et al. (1993). Physiologic, biochemical constants and partition coefficients used in the model are shown in Table 2-10 Physiologic constants (organ volume, blood flows, etc.)

2. HEALTH EFFECTS

Table 2-10. Parameters Used in the Shyr PBPK Model^a

Parameters for the rat	Value
Body weight (kg)	0.288
Percentage of body weight	
Liver	3.0
Fat	11.0
Skin included in application site	0.5
Skin not included in application site	9.5
Muscle	56.0
Gastrointestinal tract	3.0
Richly perfused tissues	4.6
Other	12.4
Flows (L/hour)	
Alveolar ventilation	15.1
Cardiac output	18.9
Percentage of cardiac output	
Liver	5.0
Muscle	9.6
Fat	6.0
Rapidly perfused tissues	57.0
Skin included in application site	0.12
Skin not included in application site	2.3
Gastrointestinal tract	20.0
Partition coefficients	
Blood/air	8000
Liver/blood	0.9
Fat/blood	0.7
Rapidly perfused tissues	0.9
Gastrointestinal/blood	0.9
Skin/blood	0.9
Muscle/blood	0.9
Biochemical parameters and rate constants	
$V_{\max,ba}$ c ($\mu\text{mol}/\text{hour}$)	344
$K_{m,ba}$ ($\mu\text{mol}/\text{L}$)	317
$V_{\max,eg}$ c ($\mu\text{mol}/\text{hour}$)	7.9
$K_{m,eg}$ ($\mu\text{mol}/\text{L}$)	23.2
$V_{\max,glu}$ c ($\mu\text{mol}/\text{minute}$)	48.2
$K_{m,glu}$ ($\mu\text{mol}/\text{L}$)	472

^aDerived from Shyr et al. 1993

^bIncludes tissues that are not perfused with blood (such as bone [not including marrow]), body fluids (such as gastrointestinal tract contents, urine, bile, and blood in major vessels not included in any tissue group), and hair.

ba = butoxyacetic acid; eg = ethylene glycol; glu = glucuronide; K_m = concentration at $\frac{1}{2} V_{\max}$; V_{\max} = maximum rate of metabolism

2. HEALTH EFFECTS

and tissue and blood coefficients were taken from Ramsey and Andersen (1984) or were taken from other literature sources.

Validation of the model. Since the model (Shyr et al. 1993) was developed concurrently with toxicokinetic experiments being conducted in the same laboratory, the model was used to predict the outcome of experiments that were yet to be run (Medinsky et al. 1990; Sabourin et al. 1992a, 1992b, 1993). Variables that were not predictive were modified according to the experimental data. Thus, the model was developed and refined in conjunction with the data it used for validation. The model was successful in predicting urinary metabolites from the three routes of exposure.

Target tissues. The model attempted to predict the urinary profiles of 2-butoxyethanol metabolites in rats after inhalation, oral (drinking water), and dermal exposure (Shyr et al. 1993). For 2-butoxyacetic acid, the major urinary metabolite, the values predicted by the model were in reasonable agreement with the experimental data. The exception was inhalation exposure at the high dose. The study authors indicated that the lack of agreement at the high dose for inhalation exposure may have been due to several factors, including a wide variability in the experimental data and an overestimation of the formation rate of 2-butoxyacetic acid in the liver at the high dose. For the other metabolites in the urine, ethylene glycol and 2-butoxyethanol glucuronide, the model predicted well for inhalation, oral, and dermal exposure. However, the predicted values for ethylene glycol after dermal exposure at the low dose were relatively high. Shyr et al. (1993) presented a model formulation of the metabolic pathway of 2-butoxyethanol, leading to urinary excretion (Figure 2-10). Based on the data of Medinsky et al. (1990) and Sabourin et al. (1992a, 1992b, 1993), 2-butoxyethanol was primarily metabolized to 2-butoxyacetic acid, ethylene glycol, and the glucuronide of 2-butoxyethanol. Both ethylene glycol and 2-butoxyacetic acid could be metabolized further to CO₂. The unexcreted glucuronide was also available for hydrolysis back to 2-butoxyethanol. The rates at which 2-butoxyacetic acid and ethylene glycol were metabolized to CO₂ were proposed to be less than the rates at which these metabolites were excreted in the urine, since the amount of urinary metabolites was greater than the amount of CO₂ exhaled. Based on work done with ethylene glycol (Marshall 1982), small amounts of ethylene glycol and 2-butoxyacetic acid may be bound to macromolecules, such as protein, resulting in a longer retention time in the body. In the Shyr model (Shyr et al. 1993), the major compartment for 2-butoxyethanol metabolism was the liver, based on the study of Johanson et al. (1986b). Minor amounts of glucuronide are also assumed to be formed in the skin after dermal application, but there is little data to support this assumption.

2. HEALTH EFFECTS

Species extrapolation. Shyr et al. (1993) used the human inhalation data of Johanson et al. (1986b, 1988). Pulmonary ventilation and body weight data from Johanson et al. (1986a) were used, while other kinetic parameters were the same as the rat model. The metabolic parameters were adjusted for humans (K_m and V_{max}) according to Ramsey and Andersen (1984). The model adequately predicted urinary excretion of 2-butoxyacetic acid, which was similar to that of rats. When the model was applied to human dermal exposure data (Johanson et al. 1988), it overestimated 2-butoxyacetic acid excretion in the urine by 33%, as compared to experimental data.

High-low dose extrapolation. Three doses were used for each route of administration. The model accurately predicted the outcome with exception of predicting urinary 2-butoxyacetic acid excretion after the high-dose inhalation exposure (382 μmol absorbed dose). The study authors (Shyr et al. 1993) indicated that the discrepancy may have resulted from variability in the experimental levels of urinary 2-butoxyacetic acid and because the estimates did not include a factor for the unidentified metabolites experimentally observed in rat urine after inhalation exposure. No low-dose extrapolation, mimicking doses to which most consumers would be exposed, was conducted.

Interroute extrapolation. The model (Shyr et al. 1993) accurately predicted the urinary metabolite profile of 2-butoxyethanol after inhalation, oral (drinking water), and dermal absorption in rats (Medinsky et al. 1990; Sabourin et al. 1992a, 1992b, 1993). The same set of parameters was used to predict data from all three routes of exposure. Metabolic pathways were proposed based on experimental data, and the relative significance of each pathway was quantified by fitting the model to the experimental data. The model predicted the change in profiles of urinary metabolites for different exposure routes.

The Corley Model

The Corley model (Corley et al. 1994) is an expansion of the model of human inhalation exposure by Johanson (1986). In the Corley model, disposition of 2-butoxyacetic acid was included, and the model was expanded to include data on rats, the most commonly used species in experimental toxicity tests of 2-butoxyethanol. This model was further modified on the basis of data on human metabolites and dermal absorption of 2-butoxyethanol vapor (Corley et al. 1997). Other routes of exposure, including oral, dermal, and intravenous infusion, were included (Figure 2-1 1). This is a new model, however, and has not yet been subjected to extensive testing.

2. HEALTH EFFECTS

Risk assessment. In proposing the parameters necessary for a useful model to be used in the risk assessment of 2-butoxyethanol exposure, Corley et al. (1994) indicated that since human exposure is most likely by inhalation and dermal routes, these routes should be included in a model. In addition, formation of the toxic metabolite, 2-butoxyacetic acid, should be a focus of the model. Since species differences in hemolytic sensitivity to 2-butoxyethanol are known (Ghanayem and Sullivan 1993), these differences should be factored in also. The model was reasonably successful in simulating the concentration of 2-butoxyethanol in human blood after inhalation exposure (assuming no dermal absorption), in agreement with the data of Johanson (1986). In addition, total respiratory uptake of 2-butoxyethanol, the area under the 2-butoxyethanol blood concentration-time curve, and the amount of 2-butoxyacetic acid excreted in the urine were predicted with reasonable agreement. Corley et al. (1994) suggested that risk assessments can be strengthened through the use of an internal dose factor, such as the maximum concentration of 2-butoxyacetic acid in the blood, or the area under the curve for 2-butoxyacetic acid in blood in place of the administered dose, especially in interspecies comparisons. Maximum concentration is sensitive to dose rate (e.g., gavage bolus versus drinking water), whereas the area under the curve is sensitive to saturation of metabolism and elimination.

Description of the model. To develop the model Corley et al. (1994) used several types of data, including physiological constants for rats and humans, partition coefficients for 2-butoxyethanol and 2-butoxyacetic acid in various tissues, and biochemical constants describing the metabolism of 2-butoxyethanol and excretion of 2-butoxyacetic acid. The values used are presented in Tables 2-11 and 2-12.

Partition coefficients were available from the literature for 2-butoxyethanol in blood and saline (Johanson and Dynesius 1988). Partition coefficients were determined experimentally for 2-butoxyethanol and 2-butoxyacetic acid in human blood and in the blood, liver, kidney, muscle, fat, skin, lung, stomach, small intestine, and cecum of male Fischer 344 rats (Corley et al. 1994). The metabolism of 2-butoxyethanol to 2-butoxyacetic acid was assumed to take place only in the liver through the alcohol/aldehyde dehydrogenase pathway, as described previously by Johanson (1986). A saturable metabolic pathway was added to account for all other possible pathways causing the disappearance of 2-butoxyethanol from the liver. Parameters for this pathway were estimated from the model of Medinsky et al. (1990) and scaled for humans. The assumption was made in the Corley model (1994) that 2-butoxyacetic acid was bound to proteins in the blood and was eliminated by a saturable process in the kidneys (i.e., renal acid transport) as suggested by the work of Ghanayem et al. (1990a). Incorporation of protein binding was necessary to reduce the amount of "free" 2-butoxyacetic acid available for elimination in order to closely simulate data in rats and humans. Elimination constants were estimated from the data of Ghanayem et al. (1990a). The maximum concentration (C_{max}) and the area under the curve for 2-butoxyacetic acid concentration in the blood were used as estimates of the

2. HEALTH EFFECTS

Table 2-11. Parameters Used in the Physiologically Based Pharmacokinetic Model for 2-Butoxyethanol and 2-Butoxyacetic Acid^{a, b}

Parameters	Rat	Human	Estimation method ^c
Surface area (cm ²)	267	19,000	Fixed ^d
Body weight (kg)	0.23	70	Fixed
Percentage of body weight			
Liver	2.53	3.14	Fixed ^{e,f}
Kidney (2-butoxyacetic acid model)	(0.71)	(0.44)	Fixed ^{e,g}
Lung	1.17	1.15	Fixed ^f
Fat	7.0	23.1	Fixed ^f
Muscle	37.0	42.0	Fixed ^h
Gastrointestinal tract	3.4	3.4	Fixed ^h
Skin	10.0	5.1	Fixed ⁱ
Rapidly perfused	5.1	3.71	Fixed ^g
(2-butoxyacetic acid model)	(4.39)	(3.27)	Fixed ^g
Slowly perfused	24.8	9.4	Fixed ^j
Flows (L/hour)			
Alveolar ventilation	5.06	347.9	Fixed ^f
Cardiac output	5.06	347.9	Fixed ^f
Percentage of cardiac output			
Liver (including cardiac output from the gastrointestinal tract)	25.0	25.0	Fixed ^g
Gastrointestinal tract	21.0	21.0	Fixed ^h
Kidney (2-butoxyacetic acid model)	(25.0)	(25.0)	Fixed ^g
Fat	5.0	5.0	Fixed ^g
Muscle	12.0	15.0	Fixed ^h
Skin	5.0	5.0	Fixed ^d
Rapidly perfused	51.0	50.0	Fixed ^k
(2-butoxyacetic acid model)	(26.0)	(25.0)	Fixed ^k
Slowly perfused	2	2	Fixed ^l
Partition coefficients for 2-butoxyethanol			
Blood/air	7965	7965	Fixed ^m
Liver/blood	1.46	1.46	Measured ⁿ
Kidney/blood	1.83	1.83	Measured ⁿ
Lung/blood	11.3	11.3	Measured ⁿ
Fat/blood	2.03	2.03	Measured ⁿ

2. HEALTH EFFECTS

Table 2-11 (continued)

Parameters	Rats	Humans	Estimation method ^c
Muscle/blood	0.64	0.64	Measured ⁿ
Gastrointestinal tract/blood	4.33	4.33	Measured ⁿ
Skin/blood	2.90	2.90	Measured ⁿ
Skin/air	7965	7965	Fixed ^m
Rapidly perfused blood	1.46	1.46	Measured ⁿ
Slowly perfused blood	0.64	0.64	Measured ⁿ
Partition coefficients for 2-butoxyacetic acid			
Liver/blood	1.30	1.30	Measured ⁿ
Kidney/blood	1.07	1.07	Measured ⁿ
Lung/blood	1.58	1.58	Measured ⁿ
Fat/blood	0.77	0.77	Measured ⁿ
Muscle/blood	1.31	1.31	Measured ⁿ
Gastrointestinal tract/blood	0.78	0.78	Measured ⁿ
Skin/blood	1.21	1.21	Measured ⁿ
Rapidly perfused blood	1.30	1.30	Measured ⁿ
Slowly perfused blood	1.31	1.31	Measured ⁿ
Metabolic constants			
2-Butoxyethanol-to-2-butoxyacetic acid			
K_{m1} (mg/L)	26.9	26.9	Fixed ^h
2-Butoxyethanol-to-others			
V_{max2} C (mg/hour/kg)	5	5	Fitted ^o
K_{m2} (mg/L)	0.5	0.5	Fitted ^o
Protein binding			
P (binding sites; mg/L)	164	164	Fixed ^p
K_d (dissoc. const.; mg/L)	46	46	Fixed ^p

2. HEALTH EFFECTS

Table 2-11 (continued)

Parameters	Rats	Humans	Estimation method ^e
Elimination rate constant for 2-butoxyacetic acid [in Urine]			
K_mE (mg/L)	0.5	0.5	Fitted ^g
Gavage absorption rate constants			
K_aS (hour ⁻¹) water	1.0	1.0	Fitted ^f

^aDerived from Corley et al. (1994)

^bValues in parentheses are specific for the 2-butoxyacetic acid model unless otherwise designated.

^cThe model parameters were estimated independently and held fixed (fixed), measured in independent experiments (measured), or estimated by fitting the model to the data (fitted).

^dMcDougal et al. (1990)

^eDow historical control data (rat)

^fAndersen et al. (1987)

^gCorley et al. (1990)

^hJohanson (1986)

ⁱFiserova-Bergerova (1983c)

^jTotal tissues listed represents 91% of body weight (the remaining 9% represents structural tissues with negligible blood perfusion). For mass balance, the volume of slowly perfused tissues (% body weight) was assumed to be 91 - (sum of other tissues).

^kFor mass balance, blood flow to rapidly perfused tissues (% cardiac output) was assumed to be 100 - (sum of other tissues).

^lBlood flow to slowly perfused tissues from Corley et al. (1990) after accounting for muscle and skin.

^mJohanson and Dynesius (1988). Skin:air assumed to be equal to blood:air.

ⁿDetermined *in vitro* using ultrafiltration (Jepson et al. 1992).

^oEstimated by fitting model to data of Medinsky et al. (1990).

^pRussell et al. (1987)

^qEstimated by fitting model to data of Ghanayem et al. (1990a).

^rEstimated by fitting model to data from Figure 3 and Tables 5 and 6.

2. HEALTH EFFECTS

Table 2-12. Human Physiological Parameters Adjusted for Light-to-Moderate Exercise^{a,b}

Parameters	Value
Flows (L/hour)	
Alveolar ventilation	1,322
Cardiac output	603
Percentage of cardiac output	
Liver (including gastrointestinal)	16
Kidney (2-butoxyacetic acid model)	(11)
Fat	6
Muscle ^c	42
Gastrointestinal tract	12
Skin ^c	3
Rapidly perfused tissue (2-butoxyacetic acid model)	32 (21)
Slowly perfused tissue	1

^aDerived from Corley et al. 1994

^b50 watts on bicycle ergometer

^cMuscle and skin compartment of Johanson (1986) described separately and kidney compartment added for the BAA model. Blood flows to these compartments were adjusted according to Astrand (1983).

2. HEALTH EFFECTS

“internal dose” or “delivered dose” for extrapolations between species, routes, and high and low doses. Concentration-response relationships for 2-butoxyacetic acid-induced hemolysis in rat and human blood have been shown (Bartnik et al. 1987; Ghanayem 1989; Ghanayem et al. 1987, 1992; Udden 1994).

Validation of the model. The reliability of the model was tested using data sets reported by several laboratories, in addition to data produced by Corley et al. (1994). Data from previous reports were used to derive estimates of biochemical parameters describing dermal uptake of 2-butoxyethanol by humans (Ghanayem et al. 1990a; Johanson and Boman 1991; Medinsky et al. 1990). Validation of these parameters was performed by comparing model predictions with other studies having relevant data. A simulation was conducted of 2-butoxyethanol and 2-butoxyacetic acid concentrations in the blood of young and old rats dosed intravenously with 2-butoxyethanol. Reasonable agreement was obtained for simulations for the younger rats. The model tended to overpredict the concentration of 2-butoxyacetic acid at low doses soon after administration but was adequate thereafter. In older rats, adjustments to the parameters, including increasing the volume of the fat compartment, and reducing the rate of elimination of the kidneys to simulate the renal disease common in aged rats, improved the simulations.

The parameters associated with the disposition of 2-butoxyacetic acid were validated against experimental data produced by Corley et al. (1994). Reasonable agreement was reached for 2-butoxyacetic acid in the blood. Model simulations of the amounts of 2-butoxyacetic acid excreted by young male rats (16-18 weeks) and older rats (12 or 13 months) were compared with the data of Ghanayem et al. (1987a, 1987b). The best predictions were for young rats at doses where hemolysis did not occur. The model did not adjust for the toxic effects of the compound on the kidney or liver that may have been secondary to the hemolytic effect. The Corley model was responsive to the normal changes in age and weight in animals.

The Corley model achieved reasonable agreement between simulations and experimental data on 2-butoxyacetic acid excreted in the urine of rats after exposure to 2-butoxyethanol in the drinking water (Medinsky et al. 1990). Excellent agreement was also reached with the data of Sabourin et al. (1992a) after inhalation exposure of rats, for respiratory uptake of 2-butoxyethanol, total amounts of 2-butoxyethanol metabolized, and total amounts of 2-butoxyacetic acid excreted. The exception was for the total amount of 2-butoxyacetic acid excreted at the high dose, which caused hemolysis in the experimental animals (Sabourin et al. 1992a). The model over-predicted the amount excreted, another indication that the PBPK model did not account for hemolytic toxicity.

2. HEALTH EFFECTS

Simulations of the human inhalation data of Johanson et al. (1986a) for the concentration of 2-butoxyethanol in the blood were comparable to the original data, assuming no dermal uptake. Instead of using a standardized weight, the actual body weights of the volunteers in the study were used, and the parameters were scaled by body weight for each. The predicted pulmonary ventilation rate for the volunteers who engaged in light exercise agreed with those observed (Johanson et al. 1986a). Reasonable agreement was also obtained for respiratory uptake, area under the curve for 2-butoxyethanol blood concentration-time, and the amount of 2-butoxyacetic acid excreted in the urine. Simulations of the data of Johanson and Boman (1991), including dermal uptake through exposure to the vapor, suggested that dermal uptake was not as important as was indicated by Johanson and Boman (1991). When the assumption was made that the finger prick blood samples taken in the Johanson and Boman (1991) study were venous blood samples draining the skin, rather than mixed arterial blood, the model adequately predicted the data (Corley 1996). Data from an additional dermal exposure study, in which volunteers were exposed one arm only to 50 ppm 2-butoxyethanol for 2 hours and in which blood samples were taken from the unexposed arm (Corley et al. 1997) confirmed this theory. The Corley model was further refined by changing it to better reflect human metabolism as measured by urinary metabolite levels in Corley et al. 1997, and using a new permeability coefficient for dermal absorption of vapors. The model was changed to make a majority of total urinary butoxyacetic acid in the form of the glutamine conjugate and to eliminate urinary excretion of free and conjugated butoxyethanol and free or conjugated ethylene glycol or its metabolite, glycolic acid.

Target tissues. Reasonable agreement was achieved between the model and experimental data for 2-butoxyacetic acid levels in the blood of rats after gavage exposure and in the urine of rats after drinking water exposure, respiratory uptake of 2-butoxyethanol, total amount metabolized, and total 2-butoxyacetic acid excreted after inhalation exposure of rats, as long as the doses were below those that caused hemolysis. In humans, reasonable agreement was achieved between the model and experimental data for respiratory uptake, the area under the curve for 2-butoxyethanol blood concentration-time, and the amount of 2-butoxyacetic acid excreted in the urine after inhalation exposure (Corley et al. 1994).

Species extrapolation. To compare species, Corley et al. (1994) ran simulations of the maximum concentration and area under the curve for 2-butoxyethanol and 2-butoxyacetic acid in rat and human blood after a 6-hour dermal exposure to aqueous 2-butoxyethanol. A 10% body surface exposure was assumed, with no evaporation of the chemical. Maximum absorption was predicted at 40% solutions, with less absorbed at higher and lower doses. Although the reasons for these results are not clear, they suggest that under normal circumstances, humans are unlikely to absorb enough 2-butoxyethanol through dermal exposure alone to cause

2. HEALTH EFFECTS

hemolysis. Following inhalation exposure, the model predicts that humans would not be expected to produce enough 2-butoxyacetic acid to result in hemolysis even if they were exposed to concentrations up to 1,160 ppm 2-butoxyethanol, the saturated vapor concentration (Corley 1996). This conclusion was reached even with the inclusion of dermal absorption of vapor, the estimate of which was subsequently reduced on the basis of Corley et al. (1997) human dermal absorption data.

High-low dose extrapolation. The model seems to predict well for animals at low and middle doses that do not cause hemolysis for oral (drinking water) and inhalation exposure (Medinsky et al. 1990; Sabourin et al. 1992a). The model was not designed to adjust for toxicity in the kidney and liver that may have been secondary to the hemolytic effects of 2-butoxyethanol. Low dose extrapolation, modeling doses similar to those at which most consumer exposure occurs, was not conducted.

Interoute extrapolation. The model seemed to predict well for different routes of exposure in animals, as long as the doses were below those causing hemolysis. The model predictions did not agree with human dermal absorption estimations of Johanson and Boman (1991) when it was assumed that finger prick blood samples represented arterial blood. The model predictions did agree with human data when it was assumed that finger prick blood samples represented venous blood draining the skin, and they predicted the one arm-only exposure scenario (Corley 1996). Human inhalation exposure was predicted well (Johanson et al. 1986a).

2.4 MECHANISMS OF ACTION

2-Butoxyethanol toxicity has been studied in some detail, and current understanding of 2-butoxyethanol includes its metabolic fate, mechanism of toxicity, pharmacokinetic models for disposition, and impact of exposure on human health. These aspects of 2-butoxyethanol toxicity will be addressed in the following sections. The toxicity of 2-butoxyethanol acetate has been studied far less than 2-butoxyethanol toxicity, presumably because 2-butoxyethanol acetate is assumed to be metabolized to 2-butoxyethanol in the body.

2.4.1 Pharmacokinetic Mechanisms

Pharmacokinetic models of 2-butoxyethanol disposition have been developed (Bartnik et al. 1987; Corley et al. 1997; Corley et al. 1996; Corley et al. 1994; Ghanayem et al. 1990a; Medinsky et al. 1990; Sabourin et al. 1992a, 1992b, 1993; Shyr et al. 1993). Both *in vivo* and *in vitro* data indicate that metabolic activation of

2. HEALTH EFFECTS

2-butoxyethanol by the alcohol/aldehyde dehydrogenases is a prerequisite for the development of the characteristic hematotoxicity (Dow 1982; Ghanayem et al. 1987b, 1987c; ICI 1989). Metabolism is presumed to take place in the liver; excretion takes place primarily via the urine.

2-Butoxyethanol metabolism to its reactive intermediate, 2-butoxyacetic acid, presumably through the intermediate 2-butoxyacetaldehyde, takes place through oxidation by the alcohol/aldehyde dehydrogenases. Nontoxic pathways include conjugation of 2-butoxyethanol with glucuronic acid, which is excreted in the urine; thus, the conjugate formation leads to elimination and the prevention of formation of toxic metabolites. Some evidence exists that ethylene glycol is also a metabolite of 2-butoxyethanol under certain circumstances through dealkylation; ethylene glycol formation may depend on the route of administration (Corley et al. 1994; Medinsky et al. 1990; Rambourg-Schepens et al. 1988; Sabourin et al. 1992a, 1992b, 1993; Shyr et al. 1993). At higher doses, saturation of the 2-butoxyacetic acid and ethylene glycol pathways favors the formation of glucuronide conjugates of 2-butoxyethanol (Sabourin et al. 1992a). Ethylene glycol itself has been shown to cause hepatic, renal, and developmental toxicity, as summarized in the ATSDR *Toxicological Profile for Ethylene Glycol and Propylene Glycol* (ATSDR 1993). However, ethylene glycol is a minor metabolite of 2-butoxyethanol, and the toxicity of 2-butoxyethanol in humans and animals can be understood on the basis of on its metabolism to 2-butoxyacetic acid.

2.4.2 Mechanisms of Toxicity

The most characteristic toxic effect of 2-butoxyethanol in animal models is on the hematologic system and includes elevated osmotic fragility of erythrocytes, hemolysis, decreased hematocrit, hemoglobinuria, hemoglobinemia, and hemolytic anemia (Bartnik et al. 1987; Carpenter et al. 1956; Corley et al. 1994; Dodd et al. 1983; Dow 1959; Duprat and Gradiski 1979; Eastman Kodak 1983; Ghanayem and Sullivan 1993; Ghanayem et al. 1987a, 1987b, 1990b, 1992; Grant et al. 1985; Hardin et al. 1984; Krasavage 1986; Nagano et al. 1979, 1984; NTP 1993, 1989; Sabourin et al. 1992a, 1992b, 1993; Union Carbide 1980a). Evidence of the early stages of hemolysis, characterized by erythrocytic swelling and detected as increased mean cell volume, increased hematocrit, and decreased mean cell hemoglobin concentration, has also been observed after exposure to 2-butoxyethanol (Bartnik et al. 1987; Dodd et al. 1983; Ghanayem and Sullivan 1993; Tyl et al. 1984). These effects have also been observed after 2-butoxyethanol acetate exposure (Truhaut et al. 1979). Compensatory erythropoiesis, occurring in response to hemolysis, results in an increase in reticulocytes, increased mean cell volume, increased or normal mean cell hemoglobin, and decreased mean cell hemoglobin concentration (McGrath 1993); it may also contribute to changes in hematological parameters, as was evident

2. HEALTH EFFECTS

in some animal studies of 2-butoxyethanol (Dodd et al. 1983; Ghanayem et al. 1987a, 1992; Grant et al. 1985; NTP 1989; Tyl et al. 1984).

Hemolysis can occur within the circulatory system, or outside the circulatory system in the spleen, bone marrow, or liver (McGrath 1993). Hemoglobinemia (the presence of free hemoglobin in the blood) and hemoglobinuria (the presence of free hemoglobin in the urine) are indicators of destruction of red blood cells within the circulatory system (Jones and Hunt 1983; McGrath 1993). Hemoglobin is normally contained in erythrocytes. When hemoglobin is released from damaged erythrocytes, it is detectable in the blood, is normally decomposed in the spleen and other organs of the reticula-endothelial system, and is eliminated as bilirubin. When the amount of free hemoglobin in the blood is such that the spleen and other organs of the reticula-endothelial system cannot completely remove it from the circulation, it appears in the urine (hemoglobinuria). When hemoglobinuria is detectable, it is reasonable to assume that hemolytic anemia is occurring. Hemoglobinuria is normally identified by the brownish or reddish-brown color of the urine (Jones and Hunt 1983). Increased hemosiderin, resulting from free hemoglobin in the circulatory system, may also be present in the kidney tubules (McGrath 1993). Hemolysis occurring outside the circulatory system is characterized by increased spleen size and weight, and hemosiderin deposits in the spleen and liver.

Most of the toxic effects of 2-butoxyethanol or 2-butoxyethanol acetate observed in animal studies may be secondary to the hemolytic effects of these chemicals. Free hemoglobin resulting from intravascular hemolysis can cause renal damage (pigment nephropathy) which may result in renal failure (Rosenstock and Cullen 1994). Hemolysis can cause accumulation of hemoglobin in renal tubular cells, and may also result in anemia, insufficient blood supply, and renal ischemic injury culminating in acute tubular necrosis. Adverse renal effects secondary to hemolysis, including tubular necrosis and other histopathological changes, have been noted in animals after inhalation (Carpenter et al. 1956), oral (Eastman Kodak 1983; Ghanayem et al. 1987a, 1987b; Krasavage 1986), or dermal exposure to 2-butoxyethanol (Duprat and Gradiski 1979; Union Carbide 1980a) and after inhalation, oral, or dermal exposure to 2-butoxyethanol acetate (Truhaut et al. 1979). Extravascular hemolysis results in accumulation of heme pigments in the liver and spleen; thus, necrosis, pigment deposition, and increased organ weight in these organs are most likely secondary to the hemolytic effects of 2-butoxyethanol (Dodd et al. 1983; Duprat and Gradiski 1979; Eastman Kodak 1983; Ghanayem et al. 1987a, 1987b; Grant et al. 1985; Krasavage 1986; NTP 1989, 1993). As a result of hemolysis, anemia and insufficient blood supply may occur, resulting in effects such as cold extremities (NTP 1989; Tyl et al. 1984) and necrosis of the tail tip (Dow 1981; Hardin et al. 1984; Nelson et al. 1984; Tyl et al. 1984).

2. HEALTH EFFECTS

Hematuria, the presence of whole red blood cells in the urine, can be identified by the reddish color of the urine (Jones and Hunt 1983). Hematuria results from hemorrhaging into the urinary system. Although hemoglobinuria and hematuria may both be present, whether or not the mechanisms of toxicity producing the two effects are related is unclear. It is possible that hematuria occurs after 2-butoxyethanol exposure via leakage of erythrocytes through renal structures that have been damaged by the presence of free hemoglobin resulting from hemolysis.

As indicated above in Section 2.3.3, metabolic activation of 2-butoxyethanol to 2-butoxyacetic acid via the alcohol/aldehyde dehydrogenase pathway is necessary for hematotoxicity. Ghanayem and coworkers (Ghanayem 1989; Ghanayem and Sullivan 1993) undertook studies to determine the mechanisms of hemolytic effects in rat and human erythrocytes *in vitro*, and to determine the relative sensitivity of human erythrocytes to 2-butoxyacetic acid. Incubation of 5 or 10 mM 2-butoxyethanol with rat blood resulted in no significant hemolysis; no evidence of 2-butoxyethanol metabolites was found (Ghanayem 1989). Incubation of rat erythrocytes with 20 mM 2-butoxyethanol resulted in hemolysis that was determined to be nonspecific in nature, because as with the 5- and 10 M doses, no metabolites of 2-butoxyethanol were detected at this higher dose. Addition of either alcohol or aldehyde dehydrogenase to whole blood with 2-butoxyethanol did not cause either hemolysis or production of 2-butoxyetbanol metabolites. Thus, the work of Ghanayem (1989) suggests that whole blood is not capable of metabolizing 2-butoxyethanol *in vitro* to 2-butoxyacetic acid, the hemolytic metabolite. Incubation of rat erythrocytes with butoxyacetaldehyde or 2-butoxyacetic acid caused time- and concentration-dependent swelling of red blood cells followed by hemolysis, which has also been observed *in vivo* (Ghanayem et al. 1990b). Butoxyacetaldehyde was less effective in causing hemolysis than was 2-butoxyacetic acid, suggesting that, although whole rat blood may contain enough aldehyde dehydrogenase to cause some conversion of the aldehyde to 2-butoxyacetic acid, the 2-butoxyacetic acid is the hemolytic agent. Addition of aldehyde dehydrogenase and its cofactors, followed by butoxyacetaldehyde, resulted in a significant increase in hemolysis, which could be decreased with the addition of cyanamide, an aldehyde dehydrogenase inhibitor, thus supporting the evidence that production of 2-butoxyacetic acid is the important step in 2-butoxyethanol-specific hemolysis (Ghanayem et al. 1989). Further experiments indicated that in rat erythrocytes, 2-butoxyacetic acid and butoxyacetaldehyde caused a decrease in blood adenosine triphosphate (ATP) concentration. The observation that 2-butoxyethanol-induced hemolysis is preceded by cellular swelling and that this was associated with the depletion of ATP, suggests that the red blood cell membrane is the target of toxicity, although the primary effect on the erythrocyte is not clear. Studies on the direct effect of 2-butoxyacetic acid on the red blood cell also suggest that the red blood cell membrane is the site of toxic insult (Ghanayem and Sullivan 1993). Human erythrocytes were relatively resistant to the effects

2. HEALTH EFFECTS

of 2-butoxyacetic acid *in vitro*, suggesting differences between the human cell membrane and that of the rat (Ghanayem 1989; Ghanayem and Sullivan 1993; ICI 1989). Studies of erythrocytes from guinea pigs, dogs, pigs, and cats indicated these species were resistant to the effects of 2-butoxyacetic acid, whereas rats, mice, and rabbit erythrocytes were susceptible (Ghanayem and Sullivan 1993; ICI 1989). Blood from mice, rats, hamsters, rabbits, and baboons exposed *in vitro* is susceptible to the hemolytic effects of 2-butoxyacetic acid, which produces time- and concentration-dependent increases in mean corpuscular volume and hematocrit at concentrations at or above 1 mM (Ghanayem and Sullivan 1993). Ghanayem et al. (1992) conducted a series of experiments on the *in vitro* effect of 2-butoxyacetic acid on blood from 2-butoxyethanol-treated rats. Red blood cells from rats exposed to 125 mg/kg 2-butoxyethanol for 3 days and allowed to recover for 7 days prior to bleeding were less sensitive to the hemolytic effects of 2-butoxyacetic acid than red blood cells from untreated rats. This work confirms the observation that young erythrocytes, formed in response to recovery from the hemolytic effects of the first exposure to 2-butoxyacetic acid, are more resistant to the hemolytic effects of 2-butoxyacetic acid than mature erythrocytes. This work suggests that chronic exposure to 2-butoxyethanol might result in tolerance since the aging erythrocytes would be lysed, and since the remaining circulating erythrocytes would be younger and more resistant to hemolysis. The resilience of newly formed red blood cells to 2-butoxyethanol exposure has been confirmed by Sivarao and Mehendale (1995). These investigators also showed that bleeding rats, which increases new red blood cell formation, provided protection against the hemolytic effects of 2-butoxyethanol.

In an effort to further elucidate the mechanism of toxicity of 2-butoxyethanol, Foster et al. (1987) dosed rats directly with 2-butoxyacetic acid once by gavage with 0, 174, 434, or 868 mg/kg/day 2-butoxyacetic acid in water. Hematuria resulted from direct exposure to a single dose of 2-butoxyacetic acid at 868 mg/kg/day, but not at 434 mg/kg/day or less. The results of this study confirmed that the metabolite of 2-butoxyethanol (i.e., 2-butoxyacetic acid) could produce hematological effects similar to those observed after 2-butoxyethanol exposure. It is unknown why such a high dose of 2-butoxyacetic acid was needed to produce hemolysis since this metabolite is thought to cause the hemolytic effects resulting from exposure to 2-butoxyethanol. It is possible that the differences in the rate of uptake and excretion of the metabolite may account for the need of a higher dose level.

Evidence of anemia has also been observed in cases of intentional human poisoning with 2-butoxyethanol (Bauer et al. 1992; Gijzenbergh et al. 1989; Rambourg-Schepens et al. 1988). It has been suggested that support with fluids (Bauer et al. 1992; Gijzenbergh et al. 1989; Rambourg-Schepens et al. 1988) and hemodialysis (Bauer et al. 1992; Gijzenbergh et al. 1989) may contribute to hematological effects in humans

2. HEALTH EFFECTS

following ingestion of large doses of 2-butoxyethanol (Udden 1996). Before hemolysis is considered as the mechanism for anemia in humans, Udden (1996) suggests that additional information regarding 2-butoxy-ethanol ingestion is needed, including review of morphology of red blood cells, reticulocyte count, mean cell volume, and tests for intravascular hemolysis (lactate dehydrogenase, haptoglobin, hemoglobinuria). Hemoglobinuria should be distinguished from myoglobinuria, a condition in which myoglobin is excreted in the urine. Myoglobin resembles blood hemoglobin but contains only one heme as part of the molecule.

Metabolic acidosis has been observed following exposure to 2-butoxyethanol. Metabolic acidosis may be due to production of lactate and 2-butoxyacetic acid (Gijzenbergh et al. 1989). Metabolic acidosis, if left uncorrected, leads to hyperventilation and renal failure, which have been identified as possible toxic sequelae to 2-butoxyethanol exposure (Gijzenbergh et al. 1989; Litovitz et al. 1991; Rambourg-Schepens et al. 1988).

No specific mechanism of toxicity has been described for other toxic effects of 2-butoxyethanol, including respiratory, cardiovascular, gastrointestinal, neurological, reproductive, and developmental effects. Respiratory effects observed in humans include irritation of the nose and throat and a slight increase in nasal mucus discharge after inhalation or dermal exposure (Carpenter et al. 1956), and pulmonary edema or respiratory insufficiency after oral ingestion (Bauer et al. 1992; Gijzenbergh et al. 1989). In animals, inhalation exposure has been shown to cause rapid and shallow breathing, audible respiration, nasal discharge, perinasal encrustation, decrease in respiratory rate, and congested or hemorrhagic lungs (Carpenter et al. 1956; Dodd et al. 1983; Dow 1986; Duprat and Gradiski 1979; Kane et al. 1980; Tyl et al. 1984). After oral exposure, dyspnea has been observed (NTP 1989; Wier et al. 1987). Some of these effects, including changes in respiratory rate and hemorrhaging of the respiratory tissues, may be related to metabolic acidosis and hemolysis, respectively. After oral exposure, humans exhibit cardiovascular effects including tachycardia and low blood pressure (Bauer et al. 1992), but similar effects have not been observed in animals. Gastrointestinal effects, including emesis, have been observed in humans, monkeys, and dogs after inhalation exposure (Carpenter et al. 1956), but the cause is unknown. Other gastrointestinal effects, including hyperkeratosis and acanthosis, and diarrhea observed in animals after oral dosing may be related to contact irritation of the gastrointestinal tissues (Eastman Kodak 1983; Krasavage 1986; NTP 1993). Hemorrhagic or red stomach or intestines observed after oral or dermal dosing in animals may be related to the hemolytic activity of 2-butoxyethanol (Union Carbide 1980a, 1980b). No mechanism has been described for neurological effects, including headache, CNS depression, and disturbed taste sensation in humans after inhalation exposure (Carpenter et al. 1956), and loss of coordination, excess salivation, and weakness in animals after inhalation, oral, or dermal exposure (Carpenter et al. 1956; Dodd et al. 1983; Dow 1959, 1972, 1981, 1986; Duprat and

2. HEALTH EFFECTS

Gradiski 1979; Eastman Kodak 1983; Hardin et al. 1984; Krasavage 1986; NTP 1989; Olin 1976; Union Carbide 1980a, 1980b; Wier et al. 1987). Coma has been observed after human poisoning (Bauer et al. 1992; Gijzenbergh et al. 1989; Rambourg-Schepens et al. 1988). With the exception of decreased pup weight observed in mice at 700 mg/kg/day (Heindel et al. 1990), developmental effects (including a decrease in viable implants and an increase in malformations in animals) reported occurred at 2-butoxyethanol doses that resulted in moderate to severe maternal toxicity (Hardin et al. 1987; NTP 1989; Tyl et al. 1984; Wier et al. 1987). Reproductive effects have been observed at doses that resulted in other adverse effects in adult animals (Hardin et al. 1987; Heindel et al. 1990; NTP 1989, 1993; Schuler et al. 1984; Tyl et al. 1984; Wier et al. 1987). Mechanisms for the reproductive and developmental effects of 2-butoxyethanol have not been identified.

Several *in vitro* studies have investigated the action of 2-butoxyethanol on cells in culture, the results of which may suggest additional or related areas of research that may lead to an explanation of 2-butoxyethanol's effect on erythrocytes. 2-Butoxyethanol has been shown to effectively block metabolic cooperation between Chinese hamster V79 cells in culture at nontoxic doses (Loch-Caruso et al. 1984). At higher doses, the cells died. Metabolic cooperation is a manifestation of the transfer of metabolites between cells coupled at a specific junction (gap junction), a process that has been implicated in cell division, morphological development, and differentiation. Disruption of this process could contribute to cellular death or dysfunction, teratogenesis, or tumor promotion. In another study, 2-butoxyethanol and 2-butoxyacetic acid were shown to be cytotoxic to Chinese hamster ovary cells in culture, as indicated by a reduction in cloning efficiency (Jack et al. 1985). In support of this observation, the study authors cited the work of others, Loch-Caruso et al. (1984) and Johnson et al. (1984), who observed that 2-butoxyethanol exposure resulted in developmental toxicity of the hydra. Jackh et al. (1985) also noted that the hemotoxicity of 2-butoxyethanol observed in small rodents *in vivo* and *in vitro* (Ghanayem et al. 1987a, 1987b, 1989, 1992) also suggests cytotoxicity. In another study, 2-butoxy-ethanol was shown to decrease maximum calcium uptake by rabbit sarcoplasmic reticulum vesicles and to markedly increase the subsequent calcium efflux rate (Mayahara et al. 1982). In addition, 2-butoxyethanol caused tetany in an isolated phrenic nerve-diaphragm preparation of the rat. The significance of these results with regard to *in vivo* toxicity is currently unknown.

2. HEALTH EFFECTS

2.4.3 Animal-to-Human Extrapolations

Recent physiologically based pharmacokinetic models have tried to address 2-butoxyethanol metabolism and disposition in an effort to derive animal-to-human extrapolations (Medinsky et al. 1993; Shyr et al. 1993). Other models have also been developed based on human data (Johanson 1986,1991a; Johanson and Naslund 1988). Each model was multicompartmental and attempted to relate the generation of metabolites to end points of 2-butoxyethanol toxicity. Primary focus has been on absorption from the respiratory system and the skin (Johanson 1991a; Shyr et al. 1993). Absorption from the gastrointestinal tract has also been addressed (Shyr et al. 1993). Additional data have recently been published to more adequately model the metabolism and disposition of 2-butoxyethanol in rats (Johanson 1994), as well as additional animal and human data and revised modeling parameters that more adequately address issues of routes of exposure and competing metabolic pathways (Corley et al. 1997; Corley et al. 1994). With this additional work, the database and resulting model are more complete, and come close to adequately modelling data for both animals and humans. Additional study, including regarding dermal uptake, protein binding parameters, renal elimination, mechanism of hemolysis of rat erythrocytes and its relevance in humans, and further evaluation of the metabolism and kinetics of 2-butoxyethanol and its metabolites in animals with erythrocytic sensitivity similar to humans (less sensitive than rats), has been recommended to improve the ability of the model to predict outcome in different species (Corley et al. 1994).

In vitro studies have shown that, compared to rat blood cells, human red blood cells are insensitive to the hemolytic effects of 2-butoxyacetic acid. Concentrations of 2-butoxyacetic acid that caused hemolysis of rat red blood cells did not cause hemolysis of human red blood cells (Bartnik et al. 1987). For example, following a 60-minute exposure of rat red blood cells to 7.5 mM 2-butoxyacetic acid, 100% hemolysis was observed. Following a 60-minute exposure of human red blood cells to 15 mM 2-butoxyacetic acid, no hemolysis was observed (Bartnik et al. 1987). An *in vitro* study measuring more sensitive end points of red blood cell effects, i.e., mean cell volume and hematocrit, has also shown rat red blood cells to be more sensitive to 2-butoxyacetic acid compared to human red blood cells (Ghanayem and Sullivan 1993). For example, following a 1-hour exposure to 2 mM 2-butoxyacetic acid, mean corpuscular volume was about 150% of controls in rat red blood cells and 105% of controls in human red blood cells; hematocrit was about 155% of controls in rat red blood cells and 105% of controls in human red blood cells. Red blood cells of rabbits, hamsters, mice, and baboons were also sensitive to 2-butoxyacetic acid, while red blood cells of cats, pigs, dogs, and guinea pigs were not sensitive to 2-butoxyacetic acid (Ghanayem and Sullivan 1993). The molecular mechanism for the resistance of red blood cells from some species but not others is not known. Until the mechanism is known, it

2. HEALTH EFFECTS

has been suggested that 2-butoxyethanol should be treated as a chemical with the potential for causing human toxicity (Ghanayem 1996).

2.5 RELEVANCE TO PUBLIC HEALTH**Overview**

2-Butoxyethanol and, to a lesser extent, 2-butoxyethanol acetate are found in a wide variety of industrial and consumer products. For 2-butoxyethanol, the exposure scenario of most concern to the general public is inhalation or dermal absorption while using household cleaners, metal cleaners, spray lacquers, quick-dry lacquers, enamels, varnishes, varnish removers, and latex paints. 2-Butoxyethanol acetate is used in nitrocellulose lacquer, epoxy and acrylic enamels, latex coatings, and some ink and spot remover formulations. Individuals employed in industries that make or use 2-butoxyethanol or 2-butoxyethanol acetate (e.g., hospitals and medical facilities, silk screen shops, furniture finishers, print shops, paint manufacture) are probably exposed to the highest concentrations of atmospheric 2-butoxyethanol or 2-butoxyethanol acetate. In the general population, people residing around certain chemical manufacturing sites or living near waste sites containing 2-butoxyethanol or 2-butoxyethanol acetate may theoretically be exposed to concentrations higher than background air concentrations; however, neither of these chemicals has been measured in air near NPL sites.

Several *in vivo* and *in vitro* studies have conclusively demonstrated that 2-butoxyethanol and 2-butoxyethanol acetate can be absorbed through human skin. Dermal absorption can occur from exposure to the liquid form and small amounts of the vapor can be absorbed dermally. Since over half of the products containing 2-butoxyethanol marketed in the United States are intended for household use, the potential for dermal exposure is great. All-purpose cleaners comprise the largest proportion of consumer products containing 2-butoxyethanol. Consumers generally do not wear respiratory protection or protective gloves when performing general cleaning chores such as washing windows, mopping floors, cleaning cars, etc. Thus, the potential for exposure through both the dermal and inhalation routes is substantial.

Occupational exposure to 2-butoxyethanol usually involves co-exposure to other solvents and chemicals. In several NIOSH Health Hazard Evaluations, effects reported by workers included eye, nose, and throat irritation; coughing; runny nose; headache; dizziness; lightheadedness; and nausea. Since personal breathing zone and workplace air samples analyzed for solvents and other chemicals (such as toluene, xylene, methyl

2. HEALTH EFFECTS

ethyl ketone, methyl isobutyl ketone, styrene) along with 2-butoxyethanol indicated that exposure levels for each chemical were below the NIOSH, ACGIH, and OSHA criteria, NIOSH concluded that the effects were probably due to the additive combination of the solvents.

Acute oral exposures of humans to large amounts of 2-butoxyethanol have been shown to cause coma and respiratory depression, in addition to hematotoxic effects. Although this route of exposure is the least likely for the general population, the existence of many household products containing 2-butoxyethanol or 2-butoxyethanol acetate makes accidental poisoning a potential problem, particularly for children.

Acute- and intermediate-duration inhalation, oral, and dermal exposures to 2-butoxyethanol have been shown to cause death in animals. There is a report of human death following the ingestion of an unknown amount of cleaner containing 6.5% 2-butoxyethanol. Only scanty data are available for 2-butoxyethanol acetate. These data suggest that in animals 2-butoxyethanol acetate may be less lethal than 2-butoxyethanol. No studies were located regarding death in humans or animals after exposure to 2-butoxyacetic acid by any route.

The most noted systemic effect in animals resulting from acute and intermediate exposure to 2-butoxyethanol or 2-butoxyethanol acetate is hematotoxicity. Hemolysis occurs in several stages, including swelling, popping, reduction in volume, and hemoglobin leakage. Some or all of these stages have been observed in at least three cases of human poisoning and in animal studies. Hemodialysis may have contributed to the hemolytic effects in humans. The hematotoxicity is characterized in humans by decreased hemoglobin content, progressive erythropenia, and hemoglobinuria, and in animals by swelling of the erythrocytes, followed by hemolytic anemia, and decreases in circulating red blood cells, hemoglobin concentration, and hematocrit. A causal relationship has been established for animals, with the proposed target being the red blood cell membrane. Hemoglobinuria observed in animals is a consequence of the hemolytic effects of the 2-butoxyethanol metabolite, 2-butoxyacetic acid. An *in vitro* study has shown that the red blood cells of rats, mice, hamsters, rabbits, and baboons are more susceptible to the hemolytic effects of 2-butoxyacetic acid than the red blood cells of guinea pigs, dogs, pigs, and cats. In contrast to animals, human red blood cells appear to be more resistant to the hemolytic effects of 2-butoxyacetic acid, although presumably the same mechanism is operational in humans.

Other notable systemic effects observed in humans exposed to high doses include respiratory depression, metabolic acidosis, alteration of cardiac rhythm, and hematuria. In animals, hepatic and renal toxicity have been observed, including hepatic necrosis and hemoglobin casts in the renal tubules and hematuria. Increased

2. HEALTH EFFECTS

spleen weight and splenic congestion have been observed after 2-butoxyethanol exposure in animals. Many of the effects observed may be due to the hemolytic effects of 2-butoxyethanol.

Data on effects of 2-butoxyethanol and 2-butoxyethanol acetate on male reproductive tissues in animals generally indicate that male reproductive organs are not affected, but one study indicated decreased sperm concentration in rats after intermediate-duration oral exposure to 2-butoxyethanol. However, no significant effects on spermatid heads (10^7 /g testis), spermatid counts (mean/ 10^4 mL), or percent mobile spermatozoa were observed. Reproductive effects in female animals consist of vaginal bleeding and altered estrous cycles. Data on reproductive and developmental competence in animals indicate that at sufficiently high doses, especially those that result in adult animal toxicity, 2-butoxyethanol can adversely affect these processes. Reduced fetal viability and retarded skeletal ossification were the most frequently observed effects.

Limited *in vitro* data indicate that 2-butoxyethanol is not genotoxic. No studies were located regarding cancer in humans or animals after exposure to 2-butoxyethanol.

In studies of 2-butoxyethanol exposure in humans, the information provided on exposure levels and their correlation with observed effects were sufficient for derivation of a chronic inhalation MRL. Data from animal studies were used to derive other MRL's.

Minimal Risk Levels for 2-Butoxyethanol

Inhalation MRLS

- An MRL of 6 ppm has been derived for acute-duration inhalation exposure (14 days or less) to 2-butoxyethanol.

The MRL was calculated from a NOAEL of 50 ppm for hematotoxicity in pregnant rats in a study by Tyl et al. (1984). See Appendix A for details. In the study by Tyl et al. (1984), timed-pregnant Fischer 344 rats (n=36) were exposed to 2-butoxyethanol vapors by inhalation on gestational days 6-15 at concentrations of 0, 25, 50, 100, or 200 ppm for 6 hours per day. The animals were observed for clinical signs throughout the study, and food and water consumptions (withheld during exposures) was measured. Maternal body weights were taken on gestational days 0, 6, 9, 12, 15, and 21. The animals were sacrificed on gestational day 21 after blood samples were collected. Hematology and organ weights (uterus, liver, thymus, spleen, and kidney) were evaluated.

2. HEALTH EFFECTS

Hematologic determinations on dams (at 100 and 200 ppm but not 50 ppm) showed statistically significant reductions in erythrocyte (red blood cell) count and mean corpuscular hemoglobin concentration, and an increase in hemoglobin per cell (mean corpuscular hemoglobin) and size of the red blood cell (mean corpuscular volume). There were significant increases in hemoglobin and hematocrit at 200 ppm. Clinical signs that occurred with an incidence different from the controls were observed in 75% of dams in the 200-ppm group during the exposure period. They included the clear evidence of hematuria or hemoglobinuria, periocular wetness, perinasal encrustation, pale and cold extremities, and necrosis of the tail tip. Periocular wetness, clear evidence of hematuria, and perinasal discharge were also noted in 25-50% of the dams in the 100-ppm group. In the 25- and 50-ppm groups, 25% of the dams showed signs of periocular wetness. Maternal body weight gain was decreased 29% in the 100-ppm group at gestational days 6-15, compared to the control group. Exposure resulted in negative weight gain (weight loss during specific periods of time, at 200 ppm), decreased maternal body weight (gestational days 6-21, 11-12% at 200 ppm), decreased food consumption (gestational days 6-15, 13% at 100 ppm), and evidence of anemia (200 ppm) that was not observed at lower concentrations. Decreased water consumption (14%) was noted at 200 ppm. There was a reduction in maternal gravid uterine weight at 200 ppm. Relative kidney weight was elevated compared to controls at 200 ppm in the presence of decreased body weight. No treatment-related effects were observed on the weights of the liver.

Although periocular wetness was observed at high incidences in the rats at ≥ 25 ppm, indicating that 25 ppm is a minimal LOAEL for eye irritation (from direct contact of the eyes with the vapor during inhalation exposure), hemolysis is the most consistently observed critical effect of concern for exposure to 2-butoxyethanol.

Other studies have shown hematotoxicity after acute inhalation exposure at similar concentrations. Fischer 344 rats (eight males, eight females) were exposed for 9 days, 6 hours per day, 5 days per week to 2-butoxyethanol target concentrations of 0, 25, 100, or 250 ppm (mean average concentrations determined by gas chromatography to be 0, 20, 86, or 245 ppm, respectively) (Dodd et al. 1983). Rats were observed for signs of toxicity during exposure and for 14 days postexposure. Necropsies were performed on animals that died and on survivors killed at the end of the observation period. Biological assessments included daily animal observations, determination of body and organ weight (kidney, liver, lungs, and testes), and ophthalmologic, hematologic, and gross pathologic examinations. A few male rats exposed to 245 ppm were observed to have audible respiration and

2. HEALTH EFFECTS

nasal discharge. There was no effect on the hematologic parameters in rats exposed to 20 ppm 2-butoxyethanol. At 86 ppm, both sexes showed evidence of a significant, but less profound, effect on the erythroid parameters. At 245 ppm, both male and female rats showed significantly depressed red blood cell counts (20% below control values), hemoglobin, and mean corpuscular hemoglobin concentration, and significant increases in mean corpuscular volume, nucleated red blood cells, and reticulocytes. Red stained urine (hematuria) was also observed in rats of both sexes exposed to 245 ppm. Female rats exposed to 86 ppm showed significantly increased liver weights. Male and female rats of the 245 ppm group also showed increased liver weights. Decreased mean body weight gains (percentage not provided) were also found. A 14-day postexposure recovery showed substantial reversal of the affected blood parameters.

- An MRL of 3 ppm has been derived for intermediate-duration inhalation exposure (15-364 days) to 2-butoxyethanol.

The MRL was derived from a NOAEL of 25 ppm for hematotoxicity in female rats in a study by Dodd et al. (1983). See Appendix A for further details. The female rat was used since females appeared to have more severe hematological effects than the male rats. In the study by Dodd et al. (1983), Fischer 344 rats (16 males, 16 females) were exposed for 90 days, 6 hours per day, 5 days per week to 2-butoxyethanol target concentrations of 0, 5, 25, or 75 ppm (mean average concentrations determined by gas chromatography were 0, 5, 25, or 77 ppm, respectively). Rats were observed for signs of toxicity during exposure and for 14 days postexposure. Necropsies were performed on animals that died and on survivors killed at the end of the observation period. Biological assessments included daily animal observations, body weight and organ (kidney, liver, lungs, and testes) weight determinations, and ophthalmologic, hematologic, and gross pathologic examinations. In addition, red blood cell osmotic fragility tests, serum chemistries, urinalyses, and histologic examinations of selected tissues of the high 2-butoxyethanol concentrations were performed. No deaths occurred throughout the study. No clinical signs of toxicity were observed. There was a transient decrease in body weight gain (exposure weeks 2-4; data not shown) of females exposed to 77 ppm 2-butoxyethanol. After 6 weeks (3 1 exposures), female rats exposed to 77 ppm had slight but significant decreases (13% below control values) in red blood cell counts and hemoglobin concentrations, accompanied by a 11% increase above control values in mean corpuscular hemoglobin. At the end of the 90-day study, the hematologic effects seen in the exposed female rats either lessened or returned to control value ranges. The only significant hematologic finding in male rats was a 5% decrease in red blood cells at 77 ppm after 66 exposures. The red

2. HEALTH EFFECTS

blood cell osmotic fragility tests of both 2-butoxyethanol-treated rats and controls were similar. No treatment-related differences were found in body weight, organ weights, urine or serum chemistries, gross lesions, or microscopic lesions in males or females. In light of the results of the Dodd et al. (1983) study of acute-duration inhalation exposure of rats to doses up to 245 ppm, and the more severe hematological effects observed, which were accompanied by changes in liver weight, respiratory effects, and decreased body weight gain, it seems reasonable to accept the hematological effects seen in the intermediate inhalation exposure experiment as being the most sensitive indicator of toxicity. No other suitable supporting studies were found.

- An MRL of 0.2 ppm has been derived for chronic-duration inhalation (≥ 365 days) to 2-butoxyethanol.

The MRL was derived from NOAEL of 0.6 ppm for decreased hematocrit and increased mean corpuscular hemoglobin concentration observed in 31 male workers exposed to an average concentration of 0.6 ppm for 1 to 6 years (Baufroid et al. 1992). See Appendix A for further details. An uncertainty factor of 3 for human variability was used because the results of *in vitro* data suggest that 2-butoxyethanol does not cause significant hemolysis of normal and potentially susceptible erythrocytes (Udden 1996). In this study, 31 male workers exposed to 2-butoxyethanol were studied. Twenty workers were exposed to an average concentration of 0.75 ppm, and 11 workers were exposed to an average concentration of 0.46 ppm. The weighted average of the means for the two groups of workers is 0.6 ppm. The workers were also exposed to methyl ethyl ketone. Studies in animals indicate that methyl ethyl ketone does not produce hematologic effects (ATSDR 1992). Exposure concentrations of methyl ethyl ketone were not provided. Twenty-one unexposed men that worked for the same company served as controls. Urine was collected before the shift and at the end of the shift and assayed for free 2-butoxyacetic acid, retinol binding protein, and creatinine. Blood was collected and assayed for red blood cell counts, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, haptoglobin, reticulocytes, and osmotic resistance. Serum alanine aminotransferase and aspartate aminotransferase were also measured.

Urinary concentrations of 2-butoxyacetic acid ranged from not detected to 1.1 mg/g creatinine before shift (average 0.3), and 0.3 to 51.4 mg/g creatinine after shift (average 12.2) in persons exposed to an average of 0.75 ppm. Urinary concentrations of 2-butoxyacetic acid ranged from not detected to 3.4 mg/g creatinine before shift (average 0.6), and 0.6 to 20.4 mg/g creatinine after shift (average 9.2)

2. HEALTH EFFECTS

in persons exposed to an average of 0.46 ppm. A significant correlation ($r = 0.55$, $p = 0.0012$) was observed between end shift urinary 2-butoxyacetic acid concentrations and 2-butoxyethanol in air. Two small but statistically significant differences in hematology values were observed: a significant decrease ($p=0.03$) in hematocrit values (43.9% exposed, 45.5% controls) and a significant ($p=0.02$) increase in mean corpuscular hemoglobin concentration (33.6 g/dL exposed, 32.9 g/dL controls). These differences are consistent with hemolysis observed in animal studies, and might be early indicators of potential adverse effects in humans. However, because the changes in both hematocrit and mean corpuscular hemoglobin concentration were in the range of normal clinical values, the effect was not considered significant. Normal clinical values of hematocrit are reported as 40-54%, with a level of 30% or less considered to indicate moderate to severe anemia (Fischbach 1992). Normal clinical values of mean corpuscular hemoglobin concentration are reported as 31-37 g hemoglobin/dL (Fischbach 1992). Increased mean corpuscular hemoglobin concentrations often indicates spherocytosis, while decreased mean corpuscular hemoglobin concentrations may indicate macrocytic anemia, chronic blood loss anemia, or pyridoxine-responsive anemia (Fischbach 1992). None of the red blood cell end points were correlated with internal exposure as assessed by free urinary 2-butoxyacetic acid and the amount of conjugated 2-butoxyacetic acid is unknown. Serum creatinine and urinary retinol binding protein were not affected. No difference was observed for serum alanine transaminase or serum aspartate transaminase. No supporting chronic-duration inhalation studies in either animals or humans were identified.

No MRLs were derived specifically for 2-butoxyethanol acetate since human and animal data are limited. Only one acute-duration inhalation study was found in the literature (Truhaut et al. 1979). The study used only one concentration (400 ppm) administered to rats and rabbits for 4 hours. Hemoglobinuria and hematuria were observed in the rabbits but not in the rats. Similarly, only one study was found in the literature for intermediate-duration inhalation exposure (Truhaut et al. 1979). The study used only concentrations of 400 ppm for 1 month and 100 ppm for 10 months in rats and rabbits, and serious effects (hemoglobinuria, hematuria, or renal nephrosis) were observed at both concentrations. No chronic-duration inhalation exposure studies of 2-butoxyethanol acetate were found in the literature. Since 2-butoxyethanol acetate is metabolized to the same toxic metabolite as is 2-butoxyethanol, it seems likely that the MRLs for 2-butoxyethanol acetate would be similar to those of 2-butoxyethanol.

2. HEALTH EFFECTS

Oral MRLs

- An MRL of 0.4 mg/kg/day has been derived for acute-duration oral (14 days or less) exposure to 2-butoxyethanol.

The MRL was derived from a LOAEL of 32 mg/kg for hematotoxicity in rats in a study by Ghanayem et al. (1987a). See Appendix A for details. In the study by Ghanayem et al. (1987a), young (4-5 weeks) and adult (9-13 weeks, 5-6 months, and 16 months) rats were dosed with 0, 32, 63, 125, 250, or 500 mg/kg 2-butoxyethanol by gavage. Hematotoxicity, metabolism, and excretion of 2-butoxyethanol were monitored for 48 hours. Animals were killed at 48 hours after treatment, and spleen, liver, kidney, testes, and urinary bladder were weighed, fixed, and examined. 2-Butoxyethanol at 125 mg/kg caused severe acute hemolytic anemia in older rats, resulting in significant decreases in red blood cells, hemoglobin, and hematocrit, and increases in the concentration of free plasma hemoglobin. Secondary to the hemolytic effects, 2-butoxyethanol also caused hemoglobinuria in 16-month-old rats at ≥ 32 mg/kg, in 6-month-old rats at ≥ 63 mg/kg, and in younger rats (4-13 weeks) at ≥ 125 mg/kg. Other effects secondary to hemolysis consisted of histopathologic changes in the liver and kidney in adult rats, including focal disseminated coagulative necrosis of hepatocytes at 250 mg/kg and hemoglobin casts in the proximal tubules of the kidney at 125 mg/kg. Relative spleen weight was drastically increased (180-230% of control values). These effects of 2-butoxyethanol were dose- and time-dependent. Both the hemolytic effects and the secondary effects of 2-butoxyethanol were age-dependent, with older rats being more sensitive than younger rats. Since the severity of hemoglobinuria in the 16-month-old rats increased as the dose levels increased and since hemoglobinuria occurred in younger rats only at higher doses, the 32-mg/kg dose was considered to be a less serious LOAEL. The use of 32 mg/kg as a less serious LOAEL for the derivation of the acute oral MRL is supported by a study in pregnant rats in which no hematological effects were found at a similar dose of 30 mg/kg/day given for 3 days during gestation (NTP 1989).

Hemolytic anemia is the characteristic toxic reaction to 2-butoxyethanol. Sperm-positive Fischer 344 rats (27-33 per dose group) were administered 0, 30, 100, and 200 mg/kg/day 2-butoxyethanol in distilled water by gavage on gestational days 9-11 (NTP 1989). The biological effects of 2-butoxyethanol on dams were assessed during treatment as well as 24 hours after treatment and on gestational day 20, and effects on fetuses were observed at sacrifice (gestational day 20); 22-24 females per group were confirmed pregnant. At sacrifice on gestational days 12 or 20, each pregnant female was examined by counting number of corpora lutea, and weighing body,

2. HEALTH EFFECTS

liver, right and left kidneys, spleen, and uterus. For females sacrificed on gestational day 20, the uterine contents were also evaluated (i.e., number of implantation sites, resorptions, and dead and live fetuses). The fetuses were sexed and examined for external and visceral malformations. Maternal and fetal blood (pooled by litter) was analyzed for red blood cell and white blood cell counts, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, and platelet count. Red blood cell counts and corresponding measures of hematocrit and hemoglobin were significantly reduced in the 100- and 200-mg/kg/day dose groups at approximately 24 hours after the final dose. Mean corpuscular hemoglobin concentration was significantly decreased in the high-dose group. The blood dyscrasia produced at approximately 24 hours after the last treatment also included increases in reticulocytes, white blood cell count, platelet count, mean corpuscular volume, and mean corpuscular hemoglobin in the 100 and 200-mg/kg/day dose groups. On gestational day 20, maternal hematological end points recovered toward control values, although a majority of values remained different from controls in the 100- and 200-mg/kg/day dose groups. Red blood cell counts measured on gestational day 20 in the 100- and 200-mg/kg/day dose groups of each treatment period were still lower than control values, but counts had increased since cessation of treatment (i.e., in the 200-mg/kg/day dose group, the red blood cell count increased to 91% of control levels by gestational day 20). Similarly, reticulocytes declined from values measured earlier in the 100- and 200-mg/kg/day dose groups but were still significantly above the control level. Corrected white blood cell counts measured on gestational day 20 after dam treatment were similar across dose groups. Platelet counts determined at the end of the study showed a significant decreasing trend with respect to dose which appeared to be determined by a nonsignificant decrease in the high dose compared to the control group. The mean corpuscular volume and mean corpuscular hemoglobin on gestational day 20 exhibited significant dose-related trends, with the values of the two highest dose groups greater than the control values. Calculated values of mean corpuscular hemoglobin concentration showed significant decreasing dose-related trends with the high-dose group values lower than controls. The changes in mean corpuscular hemoglobin concentration were significant in the high-dose group, but were relatively slight in magnitude. The maternal hematological profiles at 24 hours after final treatment and at gestational day 20 indicate that 2-butoxyethanol-induced hemolysis triggered a compensatory hematopoietic response leading to reticulocytosis. Furthermore, recovery was more complete by gestational day 20 for dams treated on gestational days 9-11 than for those exposed on gestational days 11-13.

2. HEALTH EFFECTS

In a similar experiment conducted by NTP (1989), sperm-positive Fischer 344 rats (29-31 per dose group) were administered 0, 30, 100, and 300 mg/kg/day 2-butoxyethanol in distilled water by gavage on gestational days 11-13. The biological effects of 2-butoxyethanol on dams were assessed during treatment as well as 24 hours after treatment and on gestational day 20, and effects on fetuses were assessed at sacrifice (gestational day 20). Maternal and fetal blood (pooled by litter) was analyzed for red and white blood cell counts, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, and platelet count. Red blood cell count and corresponding measures of hematocrit and hemoglobin were significantly reduced in the 100- and 300-mg/kg/day dose groups at approximately 24 hours after the final dose. Mean corpuscular hemoglobin concentration was significantly decreased in the high-dose group. The blood dyscrasia produced at approximately 24 hours after the last treatment also included increases in reticulocytes, white blood cell count, platelet count, mean corpuscular volume, and mean corpuscular hemoglobin in the 100- and 300-mg/kg/day dose groups. On gestational day 20, maternal hematological end points recovered toward control values, although a majority of values remained different from controls in the 100- and 300-mg/kg/day dose groups. Red blood cell counts measured on gestational day 20 in the 100- and 300-mg/kg/day dose groups for each treatment period were still significantly lower than control values, but counts had increased after cessation of treatment (i.e., in the 300-mg/kg/day dose group, the red blood cell count increased from about 45% of control levels at 24 hours after the final treatment to 80% of control levels by gestational day 20). Similarly, reticulocytes declined from values measured earlier in the 100- and 300-mg/kg/day dose groups, but were still significantly above the control level. Corrected white blood cell count measured on gestational day 20 after dam treatment still exhibited a significant increasing trend with respect to dose, which appeared to be determined by a nonsignificant increase in the high-dose group. Platelet counts determined at the end of the study showed a significant increase at the high dose. The mean corpuscular volume and mean corpuscular hemoglobin on gestational day 20 exhibited significant dose-related trends with the values of the two highest dose groups significantly greater than the control values. Calculated values of mean corpuscular hemoglobin concentration showed significant decreasing dose-related trends, with the high-dose group values lower than controls. The changes in mean corpuscular hemoglobin concentration with treatment, although significant at the high-dose group, were relatively slight. The maternal hematological profiles at 24 hours after final treatment and at gestational day 20 indicate that 2-butoxyethanol-induced hemolysis triggered a compensatory hematopoietic response leading to reticulocytosis. Furthermore, recovery was more complete by gestational day 20 for dams treated on gestational days 9-11 than those exposed on

2. HEALTH EFFECTS

gestational days 11-13. Thus, 30 mg/kg/day was the NOAEL for hematological effects in both experiments in the NTP (1989) study, lending support for the use of the LOAEL of 32 mg/kg for hematological effects in the aged rats in the Ghanayem et al. (1987a) study for the derivation of the acute oral MRL.

Other studies show similar effects. In a study by Corley et al. (1994), which was conducted primarily to assist in the validation of a PBPK model (see Section 2.3.5), groups of two or three male Fischer 344 rats were given radiolabeled 2-butoxyethanol at doses of 8.6 or 126 mg/kg by gavage in water. Hemolysis and hemoglobinuria were observed in the two rats given the 126-mg/kg dose, but not in the three rats given 8.6 mg/kg.

In another study (Ghanayem et al. 1992), six male Fischer 344 rats received 125 mg/kg/day 2-butoxyethanol by gavage for 1, 2, 3, 6, or 12 consecutive days. Controls received 5 mL water/kg body weight daily for 12 consecutive days. Twenty-four hours after the last dose, blood samples were collected for hematological measurements and determination of blood ATP concentration in red blood cells in order to confirm previous observations (Ghanayem 1989; Ghanayem et al. 1990b) that hemolysis is preceded by cellular swelling, resulting in increased hematocrits and mean cell volume, and ATP depletion. Spleen and liver were removed and weighed. Organ weight/100 g body weight ratios were calculated. Treatment of rats with 2-butoxyethanol daily (125 mg/kg/day) for 1-3 consecutive days resulted in a time-dependent increase in the hemolysis of erythrocytes. However, when daily treatment with 2-butoxyethanol continued beyond 3 days, the number of erythrocytes began to rebound and approached pretreatment levels within 12 days despite continued daily exposure, suggesting development of tolerance to the hemolytic effect of 2-butoxyethanol. Mean cell volumes, ATP concentration, and the number of reticulocytes increased to the 6th day and then decreased on the 12th day. Liver weight/body weight ratios were minimally affected by repeated dosing; they declined on days 3 and 6 but increased on day 12 compared to controls. Spleen weight increased in a time-dependent manner. In other studies, hematotoxic effects were observed at higher doses. For instance, hemolysis was observed in rats receiving one dose of 250 mg/kg/day; reduced red blood cell counts and hemoglobin, and increased mean corpuscular volume, reticulocytes, and mean corpuscular hemoglobin in the presence of increased liver and spleen weight were observed in rats at 500 mg/kg/day after 1 or 4 days (Ghanayem et al. 1987b; Grant et al. 1985). Hepatic and renal histopathology similar to that observed in Ghanayem et al. (1987a) at 125 mg/kg/day was also observed at 500 mg/kg/day after one dose (Ghanayem et al. 1987b).

2. HEALTH EFFECTS

- An MRL of 0.07 mg/kg/day has been derived for intermediate-duration oral (15-364 days) exposure to 2-butoxyethanol.

The MRL was derived from a LOAEL of 69 mg/kg/day for hepatic effects in male rats in a study by NTP (1993). See Appendix A for details. In the NTP (1993) study, F344/N rats (10 males, 10 females) were given targeted concentrations of 0, 750, 1,500, 3,000, 4,500, or 6,000 ppm 2-butoxyethanol in drinking water daily for 13 weeks. Actual doses, determined by the study authors from drinking water consumption and body weight data, were as follows: 0, 69, 129, 281, 367, and 452 mg/kg/day for males and 0, 82, 151, 304, 363, and 470 mg/kg/day for females. Animals were observed twice daily and weighed at the start of the studies, weekly thereafter, and at necropsy. Clinical observations were recorded weekly. Water consumption by cage was measured twice a week. Complete necropsies were performed on all animals in the base studies. The heart, liver, right kidney, lung, thymus, and right testis were weighed, examined for gross lesions, fixed or embedded in paraffin, and stained for microscopic examination. The protocol for the 13-week studies required that tissues be examined microscopically in all control animals, animals in the highest dose group with at least 60% survivors, and all animals in the higher-dose group (inclusive of early deaths and survivors). In the clinical pathology study, 20 males and 20 females per dose group were used. On days 5 and 21, blood samples were collected for the clinical pathology and hematology studies. Week-13 analyses were conducted on samples obtained from rats in the base studies. Urinalysis was done on week-13 samples collected overnight from the base study animals. In the sperm morphology and vaginal cytology evaluations, males were evaluated for necropsy body and reproductive tissue weights and spermatozoal data and females were evaluated for necropsy body weight, estrous cycle length, and percentage of cycle spent in the various stages. Hematological effects were noted at ≥ 82 mg/kg/day in females and at 281 mg/kg/day in males, but no hematological effects were found in males at 69 or 129 mg/kg/day. Hepatic effects were also noted at ≥ 82 mg/kg/day in females and at ≥ 69 mg/kg/day in males. The hepatic effects included significantly increased levels of serum alkaline phosphatase in high-dose males (452 mg/kg/day) and in females at 363 and 470 mg/kg/day, and of serum alanine aminotransferase in males at 452 mg/kg/day and in females at 363 and 470 mg/kg/day. Histological examination of livers revealed hepatocellular alterations (hepatocytes that stained more eosinophilic and lacked the amphophilic-to-basophilic granularity of the cytoplasm) at all doses (≥ 69 mg/kg/day for males and ≥ 82 mg/kg/day for females). The changes in staining may be indications of early degenerative changes in hepatocytes. Centrilobular hepatocellular degeneration was observed in males at ≥ 281 mg/kg/day and in females at ≥ 304 mg/kg/day; and brown-to-green granular pigment staining strongly positive for iron in Kupffer cell cytoplasm in

2. HEALTH EFFECTS

males at 452 mg/kg/day and in females at ≥ 151 mg/kg/day. Renal effects were also seen in males and females. Renal effects included moderate increases in blood urea nitrogen in males at ≥ 69 mg/kg/day at week 3 and at ≥ 281 mg/kg/day at week 13 and in females at ≥ 304 mg/kg/day at week 13; increases in blood creatinine in females at ≥ 304 mg/kg/day at week 13; decreases in total blood protein in males at ≥ 281 mg/kg/day at week 13 and in females at ≥ 151 mg/kg/day at weeks 3 and 13; decreases in blood albumin in males at ≥ 281 mg/kg/day at week 13 and in females at ≥ 363 mg/kg/day at week 3 and at ≥ 304 mg/kg/day at week 13; decreased urine volume in females at ≥ 82 mg/kg/day at week 13; and increased specific gravity of the urine in males at ≥ 69 mg/kg/day and in females at ≥ 151 mg/kg/day at week 13. However, histological examination of the kidneys and urinary bladder revealed no pathological lesions. No hepatic or renal effects were found in B6C3F₁ mice in the same study at ≤ 694 mg/kg/day (males) and $\leq 1,306$ mg/kg/day (females). The renal effects observed in rats may have reflected dehydration since drinking water consumption was decreased. Thus, the 69-mg/kg/day dose in male rats is a less-serious LOAEL for both hepatic and renal effects and therefore is an appropriate dose for the derivation of the intermediate oral MRL.

The only other comprehensive intermediate oral study was conducted in adult male albino rats (COBS CD (SD)BR) that were given undiluted 2-butoxyethanol by gavage in doses of 0, 222, 443, or 885 mg/kg/day, 5 days per week over a 6-week period (Eastman Kodak 1983; Krasavage 1986). Body weights and feed consumption were recorded. Clinical signs of toxicity and deviations from normal appearance and behavior were observed. Animals were checked daily for mortality, and dead animals were necropsied; tissues (lung, heart, thymus, kidneys, liver, spleen, brain, salivary glands, stomach, cecum, colon, duodenum, jejunum, ileum, pancreas, esophagus, adrenal glands, pituitary, thyroid, parathyroid, trachea, mesenteric lymph nodes, testes, epididymides, prostate, seminal vesicles, coagulating gland, bone marrow, tongue, and nasal cavities) were collected for histologic examination. Eyes were fixed in Zenker's solution. Organ weights of liver, kidneys, heart, testes, brain, and spleen were determined. The LOAEL (serious) for hematological effects was 222 mg/kg/day, and there was no NOAEL for that effect. Hepatic and renal effects associated with the hemolytic effects occurred at 443 mg/kg/day (less serious LOAEL), but not at 222 mg/kg/day, and included hemosiderin disposition and an increase in alkaline phosphatase activity.

No MRL was derived for chronic-duration oral exposure because no data were found in the literature.

2. HEALTH EFFECTS

No oral MRLs were derived for 2-butoxyethanol acetate, specifically, because human and animal data are very scarce. Only one study of acute-duration oral exposure was found in the literature (Truhaut et al. 1979). The doses used were not specified. Thus, the data were not complete enough to derive an MRL. No studies were found for intermediate- or chronic-duration oral exposure. Since 2-butoxyethanol acetate is metabolized to the same toxic metabolite as is 2-butoxyethanol, it seems likely that the MRLs for 2-butoxyethanol acetate would be similar to those for 2-butoxyethanol.

Death. No data are available on death in humans following inhalation or dermal exposure to 2-butoxyethanol or inhalation, oral, or dermal exposure to 2-butoxyethanol acetate. An 87-year-old woman died of a cardiac arrest 3 days after ingesting an unknown amount of disinfectant cleaner containing 6.5% 2-butoxyethanol (Litovitz et al. 1991). Additional case reports of humans who ingested 2-butoxyethanol at doses of 391-1,862 mg/kg suggest that death could easily occur without supportive therapy (Bauer et al. 1992; Dean and Krenzelok 1992; Gijssenbergh et al. 1989; Rambourg-Schepens et al. 1988). Coma, respiratory depression, cardiovascular effects, hematuria, hemoglobinuria, metabolic acidosis, and oxaluria have been observed in humans after ingestion of 391-933 mg/kg 2-butoxyethanol (Bauer et al. 1992; Gijssenbergh et al. 1989; Rambourg-Schepens et al. 1988).

Acute- or intermediate-duration inhalation exposure to high concentrations (≥ 200 ppm) of 2-butoxyethanol (Carpenter et al. 1956; Dodd et al. 1983; Dow 1986; Nelson et al. 1984; Sabourin et al. 1992a; Tyl et al. 1984; Werner et al. 1934a) and 2-butoxyethanol acetate (Truhaut et al. 1979) has caused death in animals. Four-hour LC_{50} values for 2-butoxyethanol were 486 ppm for male rats and 450 ppm for female rats (Dodd et al. 1983). A 7-hour LC_{50} value of 700 ppm has been reported for mice (Werner et al. 1943a). Death in animals has been reported at concentrations of 2-butoxyethanol as low as 250 ppm for 7 hours in nonpregnant female rats (Nelson et al. 1984), 200 ppm for 6 hours per day during gestation for pregnant female rabbits (Tyl et al. 1984), and 400 ppm for 7 hours per day for 1 or 2 days in male rabbits (Dow 1986). Death was also reported in rats exposed to ≥ 314 ppm, and mice and guinea pigs exposed to ≥ 376 ppm for 30 days (Carpenter et al. 1956). For 2-butoxyethanol acetate, rabbits, but not rats, died after exposure to 400 ppm intermittently for 1 month (Truhaut et al. 1979).

Death after oral exposure to 2-butoxyethanol and 2-butoxyethanol acetate has been reported in animals. Acute oral LD_{50} values for 2-butoxyethanol range from 530 to 3,000 mg/kg for rats (Carpenter et al. 1956; Eastman Kodak 1988; Nelson et al. 1984; Olin 1976; Smyth et al. 1941; Union Carbide 1980b), from 1,230 to 1,519 mg/kg for mice (Carpenter et al. 1956; Eastman Kodak 1988), from 1,200 to 1,414 mg/kg for guinea

2. HEALTH EFFECTS

pigs (Carpenter et al. 1956; Shepard 1994b; Smyth et al. 194P), and from 320 to 370 mg/kg for rabbits (Carpenter et al. 1956). Death in acute oral studies of 2-butoxyethanol has occurred at doses as low as 200 mg/kg/day for 2 days in male rats (Smialowicz et al. 1992), 150 mg/kg/day in pregnant rats (NTP 1989), 1,180 mg/kg/day in pregnant or nonpregnant mice (Hardin et al. 1987; Schuler et al. 1984), and 1,500 mg/kg in pregnant mice (Wier et al. 1987). The acute oral LD₅₀ for 2-butoxyethanol acetate in rats is reported to be 2,400 mg/kg for females and 3,000 mg/kg for males (Truhaut et al. 1979). In intermediate oral studies of 2-butoxyethanol, deaths occurred in male rats at 885 mg/kg/day (Eastman Kodak 1983; Krasavage 1986) and in female mice at $\geq 1,300$ mg/kg/day (Heindel et al. 1990; Nagano et al. 1979, 1984).

Death has also been reported in animals exposed dermally to 2-butoxyethanol and 2-butoxyethanol acetate. Acute dermal LD₅₀ values in rabbits were reported as low as 99 mg/kg 2-butoxyethanol (Duprat and Gradiski 1979) or 220 mg/kg (Dow 1959), and as high as 406-1,804 mg/kg (Carpenter et al. 1956; Eastman Kodak 1988; Olin 1976; Union Carbide 1980a, 1980b). Death has been observed in rabbits (two of six) at a dose as low as 72 mg/kg 2-butoxyethanol (Duprat and Gradiski 1979). A 4-hour dermal LD₅₀ of 2,273 mg/kg 2-butoxyethanol has been reported in female rats (Carpenter and Condra 1961). Rats exhibited 91% mortality after receiving undiluted 2-butoxyethanol on the skin four times daily (1.4 ml/day) during gestation (Hardin et al. 1984). Sixty-five percent of guinea pigs exposed to 2.0 mL 2-butoxyethanol in a single dose died within the 1st week after exposure (Wahlberg and Boman 1979). The acute dermal LD₅₀ for rabbits for 2-butoxy-ethanol acetate has been reported to fall between 4,766 and 5,957 mg/kg (Truhaut et al. 1979).

Exposure of humans to 2-butoxyethanol or 2-butoxyethanol acetate at levels found in the ambient environment or at hazardous waste sites does not seem likely to result in death. However, the existence of many household products containing 2-butoxyethanol or 2-butoxyethanol acetate makes accidental poisoning a potential problem, particularly for children.

Systemic Effects

Respiratory Effects. Respiratory effects have been observed in humans exposed experimentally to 2-butoxy-ethanol and in humans who intentionally ingested 2-butoxyethanol. No studies were located regarding respiratory effects in humans after dermal exposure to 2-butoxyethanol or after exposure by any route to 2-butoxyethanol acetate. While no adverse respiratory effects were reported after a 2-hour inhalation exposure of humans to 20 ppm 2-butoxyethanol (Johanson et al. 1986a), humans exposed for 4 or 8 hours experienced nasal irritation and increased nasal mucus discharge at 113 ppm, and nose and throat irritation at 195 ppm

2. HEALTH EFFECTS

(Carpenter et al. 1956). In humans who intentionally ingested 2-butoxyethanol, respiratory effects consisted of diffuse pulmonary edema at a dose of 650 mg/kg in a male patient who was an abuser of alcohol and had a history of trichloroethylene ingestion (Bauer et al. 1992), poor ventilation at 467-933 mg/kg in a woman (Rambourg-Schepens et al. 1988), and obstructive respiration at 391-469 mg/kg in another woman (Gijzenbergh et al. 1989).

Respiratory effects have also been observed in animals after acute- and intermediate-duration inhalation exposure; acute, but not intermediate, oral exposure; and acute, but not intermediate, dermal exposure to 2-butoxyethanol. No adverse respiratory effects have been reported in animals after inhalation, oral, or dermal exposure to 2-butoxyethanol acetate (Truhaut et al. 1979); however, the data are limited. In acute-duration inhalation studies on 2-butoxyethanol, respiratory effects consisted of rapid and shallow breathing prior to death in rats exposed to 867 ppm for 4 hours, audible respiration and nasal discharge in rats exposed intermittently to 245 ppm for 9 days (Dodd et al. 1983), perinasal encrustation in pregnant rats exposed to ≥ 100 ppm intermittently on gestational days 6-15 (Tyl et al. 1984), decreased respiratory rate in mice exposed to ≥ 153 ppm for 10-15 minutes (Kane et al. 198(a), congestion of lungs and nasal turbinates and nasal discharge in rabbits exposed to 400 ppm intermittently for 1-2 days (Dow 1986), perinasal wetness in pregnant rabbits exposed to 200 ppm intermittently on gestational days 6-18 (Tyl et al. 1984), and congestion of lungs in dogs exposed to 617 ppm intermittently for 2 days and congestion and hemorrhage of the lungs in dogs exposed to 385 ppm for 8 days (Carpenter et al. 1956). In intermediate-duration inhalation studies of 2-butoxyethanol, respiratory effects consisted of congestion and hemorrhage of the lungs in rats at 432 ppm (males) and 314 ppm (females), in guinea pigs at 376 ppm, and in dogs at 200 or 385 ppm for 30 days (Carpenter et al. 1956). Slightly increased nasal secretions were observed in two dogs exposed to 415 ppm 2-butoxyethanol 7 hours per day, 5 days per week, for 12 weeks (Werner et al. 1943b).

In acute oral studies of 2-butoxyethanol, respiratory effects consisted of rapid, shallow, or difficult breathing in rats after a single gavage dose of 2,000 mg/kg/day, a dose that resulted in the death of two of three of the treated rats (Dow 1981), or a single gavage dose of 4,510-9,019 mg/kg (Union Carbide 1980b); congested or hemorrhaged lungs at death in rats after a gavage dose of 530 mg/kg (Carpenter et al. 1956); dyspnea in pregnant rats at 600 mg/kg/day on gestational days 9-11 or 11-13 (NTP 1989); and abnormal breathing in pregnant mice at gavage doses of $\geq 1,500$ mg/kg/day on gestational days 8-14 (Wier et al. 1987). In acute dermal studies on 2-butoxyethanol, respiratory effects consisted of congestion and thickening of the alveolar walls in rabbits at ≥ 72 mg/kg (Duprat and Gradiski 1979), and orange-red lungs in rabbits given a single dose of 0.5 mL/kg 2-butoxyethanol that remained in contact with intact skin for 24 hours (Union Carbide 1980b).

2. HEALTH EFFECTS

Based on results observed in humans, it seems likely that exposures to high concentrations of 2-butoxyethanol in air of high doses of 2-butoxyethanol would cause respiratory irritation in humans. It also seems likely that oral exposures to high concentrations of 2-butoxyethanol would cause pulmonary edema, poor ventilation, and obstructive respiration. Based on results in dermal studies in animals, skin contact of humans with high doses of 2-butoxyethanol could also cause respiratory effects. Although studies on 2-butoxyethanol acetate were limited, 2-butoxyethanol acetate is readily metabolized to 2-butoxyethanol, indicating that respiratory irritation and other effects might occur in humans exposed to high doses by any route.

Cardiovascular Effects. No studies regarding cardiovascular effects were located in humans after dermal exposure to 2-butoxyethanol or after exposure to 2-butoxyethanol acetate by any route. While no cardiovascular effects, as evidenced by blood pressure and pulse rate measurements and/or electrocardiography, were observed in humans exposed by experimental inhalation exposure to 2-butoxy-ethanol at 98-195 ppm for 4-8 hours (Carpenter et al. 1956) or 20 ppm for 2 hours (Johanson et al. 1986a), case reports of intentional ingestion of household products containing 2-butoxyethanol have indicated tachycardia and low blood pressure in a patient with a history of alcohol and trichloroethylene abuse who ingested 650 mg/kg (Bauer et al. 1992) and low blood pressure in a patient who ingested 391 mg/kg (Gijzenbergh et al. 1989). An 87-year-old woman died from cardiac arrest 3 days after she ingested an unknown amount of a cleaner containing 6.5% 2-butoxyethanol (Litovitz et al. 1991). Before death she also experienced ventricular tachycardia and arrhythmias, and hypotension. Studies in animals that determined heart weights and/or that performed histological examination of the heart and/or the aorta after inhalation (Dodd et al. 1983), oral (Eastman Kodak 1983; Krasavage 1986; NTP 1993) or dermal (CMA 1983) exposure to 2-butoxyethanol or 2-butoxyethanol acetate (Truhaut et al. 1979) did not reveal any adverse effects.

Although information on cardiovascular effects in humans and animals exposed by inhalation to 2-butoxy-ethanol are limited, it is unlikely that exposure of humans to occupational and ambient environmental air levels and air levels at hazardous waste sites of 2-butoxyethanol or 2-butoxyethanol acetate would result in cardiovascular effects. Oral and dermal studies of animals exposed to 2-butoxyethanol and 2-butoxyethanol acetate also indicate little concern for human exposure in environmental and hazardous waste site scenarios. However, the case reports of human ingestion of household products containing 2-butoxyethanol indicate that caution should be taken in the cases of intentional or accidental ingestion of large quantities of 2-butoxyethanol.

2. HEALTH EFFECTS

Gastrointestinal Effects. The only information regarding gastrointestinal effects in humans after exposure to 2-butoxyethanol or 2-butoxyethanol acetate is the subjective report of occasional belching (eructation) of a male volunteer exposed to 113 ppm for 4 hours and emesis in a female volunteer exposed to 98 ppm 2-butoxyethanol for 8 hours (Carpenter et al. 1956). The subject who experienced emesis, however, believed that the emesis was due to the relatively high chamber temperature based on her personal historical experience that high temperature often caused emesis. However, emesis was observed in a dog exposed intermittently to 617 ppm 2-butoxyethanol for 2 days, a dog exposed to 385 ppm 2-butoxyethanol for 8 days, and a monkey exposed to 210 ppm for 30 days (Carpenter et al 1956). Hemorrhagic gastric ulcers were observed in rabbits exposed intermittently to 400 ppm 2-butoxyethanol for 1-2 days (Dow 1986), and congestion of the abdominal viscera was observed in rats exposed intermittently to 432 ppm (males) or 314 ppm (females) for 30 days (Carpenter et al. 1956).

In oral studies on 2-butoxyethanol in animals, gastrointestinal effects consisted of distended stomachs filled with liquid and gas, and bloody intestines in rats after single gavage doses of 2,255-9,019 mg/kg (Union Carbide 1980b); very red small intestines in rats at a single gavage dose of 2,560 mg/kg (Olin 1976); mild hyperkeratosis and acanthosis of the stomach in rats at gavage doses of 222-885 mg/kg/day for 6 weeks (Eastman Kodak 1983; Krasavage 1986); and diarrhea in rats at 452 mg/kg/day (males) and 470 mg/kg/day (females) in the drinking water for 13 weeks (NTP 1993). Moderate-to-mild necrosis and hemorrhage of the gastric mucosa was observed in guinea pigs treated with a single gavage dose of 1,000 mg/kg 2-butoxyethanol in water, a dose that also resulted in the death of one of each sex (Shepard 1994b). However, histological examination of the gastrointestinal tract revealed no pathological lesions in rats at ≤ 470 mg/kg/day or mice at $\leq 1,306$ mg/kg/day in the 13-week drinking water study (NTP 1993).

In dermal studies on 2-butoxyethanol in animals, gastrointestinal effects consisted of reddened stomachs and intestines in rabbits that died at a dose of 902 mg/kg for 6 hours (Union Carbide 1980a), orange peritonea and intestines in rats that died at a dose of ≥ 451 mg/kg for 24 hours (Union Carbide 1980b), and very dark intestines in a rabbit dosed with 1,000 mg/kg 2-butoxyethanol on abraded skin (Olin 1976). Although one rabbit that died at 50 mg/kg/day on day 15 in a 90-day dermal study had a gastric ulcer, histological examination of gastrointestinal tracts of the rabbits at ≤ 150 mg/kg/day revealed no lesions (CMA 1983). Neither the gastric ulcer nor the death was related to 2-butoxyethanol exposure.

No studies were located regarding gastrointestinal effects in humans or animals after exposure to 2-butoxy-ethanol acetate.

2. HEALTH EFFECTS

The available data in humans and animals indicate that emesis, diarrhea, and ulcers might occur in humans exposed to very high levels of 2-butoxyethanol.

Hematological Effects. Hematological effects of 2-butoxyethanol exposure include hemolysis of red blood cells, and hemoglobinuria—the detection of hemoglobin in the urine resulting from lysed red blood cells (Jones and Hunt 1983). No adverse effect on erythrocyte osmotic fragility, which has been observed in animals, was found in humans experimentally exposed by inhalation to ≤ 195 ppm 2-butoxyethanol for 4-8 hours (Carpenter et al. 1956). Statistically significant changes in hematocrit (decrease) and mean corpuscular hemoglobin concentration (increase) were reported in men occupationally exposed to 0.46-0.75 ppm of 2-butoxyethanol (Haufrond et al. 1997). The changes were small and within normal biological variability, and so are considered a NOAEL. The effects are consistent with hemolysis observed in animal studies, and they may be indicators of potential adverse effects in humans. Hematological effects in humans who ingested household cleaning agents that contain 2-butoxyethanol consisted of nonhemolytic anemia, low prothrombin time, and thrombopenia at 650 mg/kg (Bauer et al. 1992); progressive erythropenia and hemoglobinuria at 467-933 mg/kg (Rambourg-Schepens et al. 1988); and decreased blood hemoglobin at 391-469 mg/kg (Gijzenbergh et al. 1989). Hemodialysis, used in two cases (Bauer et al. 1992; Gijzenbergh et al. 1989), may have contributed to the hematological effects. No particularly sensitive population of humans has been identified; for a discussion of *in vitro* results with hypothetically sensitive human red blood cells see section 2.8 Populations That Are Unusually Susceptible.

Hematological effects of 2-butoxyethanol have been observed in animals after inhalation, oral, and dermal exposure. In inhalation studies, the hematological effects observed in animals include increased erythrocyte osmotic fragility in monkeys at 210 ppm for 30 days and at 100 ppm for 90 days, in rats at 62 ppm for 4 hours or ≥ 54 ppm for 30 days, in mice at 100 ppm for 7 hours and ≥ 100 ppm for 30-90 days, in rabbits at 125 ppm for 7 hours, and in dogs at 200-385 ppm for 8-30 days (Carpenter et al. 1956). Other hematological effects related to hemolysis included hemoglobinuria and hemin crystalluria in rats at 432 ppm for 2-8 hours, decreased red blood cell counts and hemoglobin levels in rats at 200 ppm for 7 hours per day for 9 days, hemoglobinuria in rats at 203 ppm for a single 7-hour exposure or for 7 hours per day for 30 days, at 250-800 ppm for 2-9 hours per day for 1-6 days (Carpenter et al. 1956), and at 438 ppm for 6 hours (Sabourin et al. 1992a); hemoglobinuria, reduced red blood cells and mean corpuscular hemoglobin concentration, and increased mean corpuscular hemoglobin and mean corpuscular volume in pregnant rats at ≥ 100 ppm during gestation, and increased hemoglobin and hematocrit in pregnant rabbits at 100 ppm during gestation (Tyl et al. 1984); decreased hematocrit in dogs at 100 ppm for 90 days (Carpenter et al. 1956);

2. HEALTH EFFECTS

decreased hemoglobin, increased mean corpuscular volume, and decreased mean corpuscular hemoglobin concentration in rats at 286 ppm and depressed red blood cell counts and increased nucleated red blood cells and reticulocytes at 245 ppm for 6 hours per day for 9 days (Dodd et al. 1983), and decreased red blood cell counts, hemoglobin levels, and mean corpuscular hemoglobin concentration at 77 ppm for 13 weeks (Dodd et al. 1983). Decreased hemoglobin and hematocrit, and hypochromia, polychromatophilia, and microcytosis were observed in two dogs exposed to 415 ppm 2-butoxyethanol 7 hours per day, 5 days per week, for 12 weeks (Werner et al. 1943b).

In oral studies on 2-butoxyethanol in animals, similar hematological effects have been observed, consisting of hemoglobinuria in rats at $\geq 1,500$ mg/kg (Carpenter et al. 1956); hemoglobinuria, hemolysis, and increased concentration of free hemoglobin in plasma in rats at 500 mg/kg (Ghanayem et al. 1987b); and hemolysis, including decreased red blood cell counts, increased hematocrit, packed cell volumes, and mean cell volume in rats at ≥ 125 mg/kg (Corley et al. 1994; Ghanayem et al. 1987b, 1990, 1992; Ghanayem and Sullivan 1993; Sivarao and Mehendale 1995). Similar effects related to erythrocyte hemolysis have been found in rats at 500 mg/kg/day for 4 days (Grant et al. 1985) and in pregnant rats at ≥ 100 mg/kg/day during gestation (NTP 1989). Hematological effects reflecting hemolysis have also been found in animals after intermediate-duration oral exposure to 2-butoxyethanol: decreased red blood cell counts and hemoglobin, increased mean corpuscular hemoglobin, and hemoglobinuria at ≥ 222 mg/kg/day for 6 weeks (Eastman Kodak 1983; Krasavage 1986); decreased red blood cell counts in mice at ≥ 500 mg/kg/day for 5 weeks (Nagano et al. 1979, 1984); and decreased red blood cell count, hematocrit, and hemoglobin in rats at ≥ 82 mg/kg/day in drinking water for 13 weeks (NTP 1993).

In dermal studies of 2-butoxyethanol in animals, hemolytic effects have also been found as follows: hemolysis and hemoglobinuria in rats at ≥ 260 mg/kg and increased mean corpuscular volume, decreased red blood cell count, and decreased hemoglobin in rats at 500 mg/kg applied to the skin for 6 hours (Bartnik et al. 1987); hemoglobinuria in pregnant rats at 1.4 mL/day applied during gestation (Hardin et al. 1984); increased erythrocyte osmotic fragility in rabbits after a 3-minute skin contact at 505 mg/kg (Carpenter et al. 1956); and hemoglobinuria in rabbits at ≥ 72 mg/kg on the skin for 6-24 hours (Carpenter et al. 1956; Duprat and Gradiski 1979; Union Carbide 1980a) or hemoglobinuria with hemolytic effects on erythrocytes in rabbits at 361 mg/kg/day for 11 days (Union Carbide 1980a).

Similar hemolytic effects have been observed in animals after inhalation, oral, and dermal exposure to 2-butoxyethanol acetate (Truhaut et al. 1979). Hemoglobinuria was observed in rats and rabbits exposed by

2. HEALTH EFFECTS

inhalation to 400 ppm for 4 hours per day for 1 month- Rabbits also had decreased red blood cell counts and hemoglobin concentration. In an oral study, severe hemoglobinuria was observed in rats given an unspecified single dose. A decrease in hemoglobin and red blood cell count and hemoglobinuria occurred in rabbits after dermal application of $\geq 3,191$ mg/kg 2-butoxyethanol acetate.

The hemolytic properties of 2-butoxyethanol have been found to be age-related in F344 rats, with greater sensitivity of rats 16 months old than of rats 5-6 months old, followed by rats 9-13 weeks old. Rats 4-6 weeks old were the least sensitive (Ghanayem et al. 1987a). Furthermore, *in vitro* experiments with human and animal erythrocytes indicate species-dependent sensitivity to the hemolytic effects of 2-butoxyethanol, with rodents, rabbits, and baboons more sensitive than pigs, dogs, cats, guinea pigs, and humans (Bartnik et al. 1987; Ghanayem and Sullivan 1993). In addition, an *in vitro* study showed that human erythrocytes were resistant to the hemolytic effects of 2-butoxyacetic acid, the hemolytic metabolite of 2-butoxyethanol (Udden 1994).

In addition to the hemolytic effects of 2-butoxyethanol, other hematological effects, which also appear to be age-related, were observed in young rats (4-5 weeks old) and adult rats (9-13 weeks old) at an oral dose of 500 mg/kg (Ghanayem et al. 1987a). Adult rats exhibited neutrophilic leukocytosis and mild lymphopenia within 4 hours, but not 48 hours. In young rats, an absolute increase in total leukocytes, band neutrophils, lymphocytes, and monocytes was observed at 48 hours.

In vitro data show that human red blood cells are much less sensitive to the hemolytic effects of the 2-butoxyethanol metabolite, 2-butoxyacetic acid. Concentrations of 2-butoxyacetic acid that caused hemolysis of rat red blood cells did not cause hemolysis of human red blood cells (Bartnik et al. 1987). For example, following a 60-minute exposure of rat red blood cells to 7.5 mM 2-butoxyacetic acid 100% hemolysis was observed. Following a 60-minute exposure of human red blood cells to 15 mM 2-butoxyacetic acid, no hemolysis was observed (Bartnik et al. 1987). An *in vitro* study measuring more sensitive end points of red blood cell effects (mean cell volume and hematocrit) has also shown rat red blood cells to be more sensitive to 2-butoxyacetic acid compared to human red blood cells (Ghanayem and Sullivan 1993). For example, following a 1-hour exposure to 2 mM 2-butoxyacetic acid, mean corpuscular volume was about 150% of controls in rat red blood cells and 105% of controls in human red blood cells, and hematocrit was about 155% of controls in rat red blood cells and 105% of controls in human red blood cells. Red blood cells of rabbits, hamsters, mice, and baboons were also sensitive to the red blood cell effects of 2-butoxyacetic acid, while red blood cells of cats, pigs, dogs, and guinea pigs were not sensitive to the effects of 2-butoxyacetic acid

2. HEALTH EFFECTS

(Ghanayem and Sullivan 1993). The molecular mechanism for the resistance of red blood cells in some species but not others is not known. Until the mechanism is known, it has been suggested that 2-butoxyethanol be treated as a chemical with the potential for causing human toxicity (Ghanayem 1996).

The hematological and, in particular, the hemolytic effects of 2-butoxyethanol are the most consistent and most sensitive effects observed in animals. Although humans may be less sensitive than rats and rabbits, which are the most consistently tested animals, concern exists that humans exposed to high levels of 2-butoxyethanol may develop hemolytic effects.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after exposure to 2-butoxyethanol or 2-butoxyethanol acetate by any route, or in animals after exposure to 2-butoxyethanol acetate by any route. Muscular flaccidity, which may represent neurotoxicity rather than a direct effect on the muscle, was observed in rats that died at single gavage doses of $\geq 2,560$ mg/kg and in rabbits that died after dermal doses of $\geq 1,000$ mg/kg of 2-butoxyethanol (Olin 1976). In 13-week studies, histological examination of skeletal muscle and bone revealed no pathological lesions in rats exposed intermittently by inhalation to ≤ 77 ppm (Dodd et al. 1983), in rats receiving oral doses of ≤ 470 mg/kg/day and mice receiving oral doses of $\leq 1,306$ mg/kg/day in drinking water (NTP 1993), or in rabbits exposed dermally to ≤ 150 mg/kg/day (CMA 1983).

Musculoskeletal effects are unlikely to occur in humans exposed to 2-butoxyethanol in environmental or hazardous waste site scenarios.

Hepatic Effects. No effects on serum alanine aminotransferase or aspartate aminotransferase were observed in 31 male workers exposed to 0.46-0.75 ppm 2-butoxyethanol for 1-6 years (Haufroid et al. 1997). Case reports provide evidence that 2-butoxyethanol can result in hepatic effects following high oral doses. In a man who ingested 2 doses of a concentrated glass cleaner containing 2-butoxyethanol 12 days apart, increased serum alanine aminotransferase, aspartate aminotransferase, and bilirubin were observed following the first ingestion, but not following the second ingestion (Gualtieri et al. 1995). Hepatic failure was reported in an 87-year-old woman who died of cardiac arrest 3 days after ingesting an unknown volume of glass cleaner containing 6.5% 2-butoxyethanol (Litovitz et al. 1991). Abnormal liver function was noted in a man who had ingested 650 mg/kg 2-butoxyethanol (Bauer et al. 1992). The man was a known alcohol and trichloroethylene abuser, which probably contributed strongly to the abnormal liver function.

2. HEALTH EFFECTS

Hepatic effects have been observed in animals after inhalation, oral, and dermal exposure to 2-butoxyethanol. In inhalation studies in animals exposed to 2-butoxyethanol, hepatic effects consisted of increased liver weight in rats exposed intermittently for 9 days to ≥ 86 ppm (females) and 245 ppm (males) (Dodd et al. 1983) or intermittently to ≥ 107 ppm for 30 days (Carpenter et al. 1956); mottled livers in rabbits exposed to 400-411 ppm intermittently for 1 or 2 days (Dow 1986); congestion of the liver in dogs exposed for 8 or 28 days to 385 ppm (Carpenter et al. 1956); and cloudy swelling of the liver in rats exposed intermittently to ≥ 314 ppm for 30 days (Carpenter et al. 1956).

In oral studies in animals exposed to 2-butoxyethanol, hepatic effects consisted of mottled livers in rats that died at gavage doses ≥ 530 mg/kg (Carpenter et al. 1956); focal coagulative necrosis of hepatocytes accompanied by phagocytized hemoglobin in adult rats, but not young rats, at ≥ 250 mg/kg (Ghanayem et al. 1987a, 1987b); dark livers in rats at 1,310 mg/kg (Olin 1976) or 2,255 mg/kg (Union Carbide 1980b); increased liver weight in rats at 125 mg/kg/day for up to 12 days (Ghanayem et al. 1992), at 500 mg/kg/day 2-butoxyethanol for 4 days (Grant et al. 1985), at 180 mg/kg/day in the drinking water for 21 days (Exon et al. 1991), at 1,540 mg/kg/day in the diet for 90 days (Carpenter et al. 1956), and at ≥ 222 mg/kg/day by gavage for 6 weeks (Eastman Kodak 1983; Krasavage 1986); decreased absolute liver weight in pregnant rats at ≥ 200 mg/kg/day during gestation (NTP 1989); and hemosiderin deposition in the liver and increased serum alkaline phosphatase levels at ≥ 443 mg/kg/day and hepatocytomegaly and increased serum alanine aminotransferase levels at 885 mg/kg/day in rats dosed for 6 weeks (Eastman Kodak 1983; Krasavage 1986). In rats treated with 2-butoxyethanol in the diet for 91-93 days, relative liver weights were increased by 25% in males at 919 mg/kg/day and by 27% in females at 976 mg/kg/day (Weil 1963). No effects on liver weight were noted at lower doses (188 mg/kg/day males, 222 mg/kg/day females), nor were any histopathological changes observed at any dose. Serum alkaline phosphatase and alanine aminotransferase levels were also increased in rats at ≥ 363 mg/kg in drinking water for 13 weeks (NTP 1993). In addition, hepatocellular alterations (hepatocytes that stained more eosinophilic and lacked the amphophilic to basophilic granularity of the cytoplasm) occurred at ≥ 69 mg/kg/day, centrilobular hepatocellular degeneration occurred at ≥ 281 mg/kg/day, and brown to green granular pigment staining strongly positive for iron in Kupffer's cell cytoplasm occurred at ≥ 151 mg/kg/day in the rats in the 13-week drinking water study. These lesions, particularly in the females, displayed both increased dose-related incidence and increased dose-related severity. None of these effects occurred in mice similarly exposed (NTP 1993).

In dermal studies on 2-butoxyethanol in animals, hepatic effects consisted of pale livers in rabbits that died after 24-hour skin contact with ≥ 406 mg/kg (Carpenter et al. 1956), congestion in the liver with necrotic foci

2. HEALTH EFFECTS

and inconstant (i.e., not always present) steatosis in rabbits that died at ≥ 72 mg/kg 2-butoxyethanol (Duprat and Gradiski 1979), mottled livers with pocked surfaces in rabbits at ≥ 451 mg/kg for 6 hours (Union Carbide 1980a) or 24 hours (Union Carbide 1980b), and discolored or pale liver in rabbits dosed with 250-1,000 mg/kg on abraded skin (Olin 1976). However, histological examination of liver and gall bladder revealed no lesions in rabbits at ≤ 150 mg/kg/day 2-butoxyethanol for 90 days (CMA 1983). In addition, no effects on liver weight were observed.

Limited data are available on hepatic effects in animals exposed to 2-butoxyethanol acetate or 2-butoxyacetic acid. Histological examination of the livers revealed no pathological lesions in rats given unspecified acute oral doses of 2-butoxyethanol acetate or in rabbits given dermal applications of $\leq 10,000$ mg/kg of 2-butoxyethanol acetate (Truhaut et al. 1979). Likewise, no histopathological lesions were found in the livers of rats dosed by gavage with ≤ 868 mg/kg 2-butoxyacetic acid (Foster et al. 1987).

The data in animals indicate that hepatic effects might occur in humans exposed to very high levels of 2-butoxyethanol.

Renal Effects- No effects on serum creatinine or urinary retinol binding protein were observed in 31 male workers exposed to 0.46-0.75 ppm 2-butoxyethanol for 1-6 years (Haufroid et al. 1997). Renal effects observed in persons who intentionally ingested household cleaning agents containing 2-butoxyethanol include albuminuria in a known alcohol and trichloroethylene abuser who ingested 650 mg/kg 2-butoxyethanol (Bauer et al. 1992); oxaluria and increased serum creatinine in a patient who ingested 467-933 mg/kg (Rambourg-Schepens et al. 1988); and hematuria in a patient who ingested 391-469 mg/kg (Gijzenbergh et al. 1989), and renal failure in an 87-year-old woman who died after ingesting an unknown amount of 2-butoxyethanol (Litovitz et al. 1991).

Similar renal effects have been observed in animals after inhalation, oral, and dermal exposure to 2-butoxyethanol, with hematuria, the detection of red blood cells in the urine (Jones and Hunt 1983) being a prevalent finding. In inhalation studies of 2-butoxyethanol in animals, renal effects consisted of evidence of hematuria (red-stained urine) and enlarged kidneys in rats exposed to ≥ 523 ppm for 4 hours or to 245 ppm, 6 hours per day for 9 days (Dodd et al. 1983); hematuria in rats exposed to 800 ppm for 3 hours (Doe 1984), to 250 ppm for 7 hours (Nelson et al. 1984), or to 100 ppm for 6 or 7 hours per day during gestation (Nelson et al. 1984; Tyl et al. 1984); evidence of hematuria in rabbits at ≥ 100 ppm for 6 hours per day during gestation (Tyl et al. 1984) or 400 ppm for 7 hours per day for 1-2 days (Dow 1986); cloudy swelling of the renal convoluted

2. HEALTH EFFECTS

tubules in rats at 432 ppm for 2 hours and in guinea pigs at ≥ 376 ppm for 7 hours per day for 30 days (Carpenter et al. 1956); congestion of the kidneys in dogs at 617 ppm for 2 days and 385 ppm for 8 days (Carpenter et al. 1956); and increased kidney weight in rats at ≥ 107 ppm and in guinea pigs at ≥ 203 ppm, 7 hours per day for 30 days (Carpenter et al. 1956).

In oral studies of 2-butoxyethanol in animals, renal effects consisted of severely congested kidneys in rats at gavage doses ≥ 500 mg/kg (Carpenter et al. 1956; Sivarao and Mehendale 1995); dark and/or enlarged kidneys in rats at 1,310 mg/kg (Olin 1976); hematuria in rats at ≥ 500 mg/kg (Dow 1959; Olin 1976; Union Carbide 1980b) and in pregnant rats at 600 mg/kg/day during gestation (NTP 1989); and increased kidney weights in rats at ≥ 500 mg/kg/day for 4 days (Grant et al. 1985) and at 1,540 mg/kg/day in the diet for 90 days (Carpenter et al. 1956), and in mice at ≥ 700 mg/kg/day in the drinking water in a continuous breeding study (Heindel et al. 1990). In a 13-week drinking water study, renal effects were found in rats, but not in mice (NTP 1993). The effects in rats consisted of increased blood urea nitrogen at ≥ 69 mg/kg/day, increased blood creatinine at ≥ 304 mg/kg/day, decreased total blood protein at ≥ 151 mg/kg/day, decreased blood albumin at ≥ 281 mg/kg/day, decreased urine volume at ≥ 82 mg/kg/day, and increased specific gravity of the urine at ≥ 69 mg/kg/day. However, histological examination of the kidneys and urinary bladders of the rats revealed no pathological lesions. In rats treated with 2-butoxyethanol in the diet for 91-93 days, relative kidney weights were increased in by 18% in males at 919 mg/kg/day, and 23% in females at 976 mg/kg/day (Weil and Carpenter 1963). No effects on kidney weight were noted at lower doses (188 mg/kg/day males, 222 mg/kg/day females), nor were any histopathological changes observed at any dose.

Renal effects that are secondary to the hemolytic effects of 2-butoxyethanol were found in rats after oral exposure, as evidenced by hemosiderin accumulation in the proximal tubules at ≥ 443 mg/kg/day by gavage for 6 weeks (Eastman Kodak 1983; Krasavage 1986) and hemoglobin casts in the proximal tubules at ≥ 125 mg/kg by gavage (Ghanayem et al. 1987a). The finding of hemoglobin casts in the proximal tubules was found to be age-related, with adult rats (≥ 9 weeks old) being more sensitive than immature rats (Ghanayem et al. 1987a). This is consistent with the age-related hemolytic effects of 2-butoxyethanol, as discussed above under Hematological Effects.

In dermal studies of 2-butoxyethanol in animals, renal effects consisted of congested kidneys in rabbits after 24-hour skin contact with ≥ 406 mg/kg (Carpenter et al. 1956); enlarged kidneys with hemoglobinuric nephrosis and interstitial reactions (secondary to hemolysis) in rabbits at ≥ 72 mg/kg for 8-hour dermal contact (Duprat and Gradiski 1979); hematuria, enlarged dark kidneys with pocked surfaces, or discolored kidneys in

2. HEALTH EFFECTS

rabbits at ≥ 451 mg/kg for 6 hours (Union Carbide 1980a) or 24 hours (Olin 1976; Union Carbide 1980b); and hematuria at ≥ 180 mg/kg/day for 9 dermal 6-hour applications (Union Carbide 1980a). In the rabbits given 9 dermal applications of 2-butoxyethanol, other renal effects consisted of increased urinary protein at 361 mg/kg/day and dimpling of the renal surface, tubular vacuolization, tubular degeneration, tubular cell hyperplasia, glomerular adhesions, and interstitial nephritis at ≥ 271 mg/kg/day (Union Carbide 1980a).

Renal effects have also been observed in animals after inhalation, oral, and dermal exposure to 2-butoxyethanol acetate and after oral exposure to 2-butoxyacetic acid. In an inhalation study of 2-butoxyethanol acetate, renal effects consisted of slight hematuria in rabbits, but not rats, exposed to 400 ppm for 4 hours; hematuria and tubular nephrosis in rats and rabbits at 400 ppm, 4 hours per day for 1 month; and tubular nephritis with tubular enlargement and Henle's loop dilation, cortical atrophy, and inflammatory fibrosis in rats and rabbits at 100 ppm, 4 hours per day for 10 months (Truhaut et al. 1979). Similar effects were seen in rats given unspecified single oral doses of 2-butoxyethanol acetate by gavage and in rabbits exposed dermally to $\geq 3,191$ mg/kg of 2-butoxyethanol acetate. Hematuria was also found in rats given a single gavage dose of 2-butoxyacetic acid at 868 mg/kg (Foster et al. 1987).

The finding of hematuria in a patient who ingested 2-butoxyethanol and the consistent finding of hematuria in animals after inhalation, oral, and dermal exposure to 2-butoxyethanol and 2-butoxyethanol acetate and after oral exposure to 2-butoxyacetic acid strongly suggests that hematuria is a concern for humans exposed to high levels of 2-butoxyethanol.

Endocrine Effects. No studies were located regarding endocrine effects in humans after inhalation, oral, or dermal exposure to 2-butoxyethanol or 2-butoxyethanol acetate. Severely hemorrhaged adrenal glands were found in a dog that died after exposure to 385 ppm for 8 days (Carpenter et al. 1956). Histological examination of the adrenal, parathyroid, thyroid, or pituitary glands showed no lesions in rats at ≤ 77 ppm, 6 hours per day, 5 days per week for 13 weeks (Dodd et al. 1983). In oral studies on 2-butoxyethanol in animals, red adrenal glands, which may be related to the hemolytic effects, were seen in rats at 2,255-9,019 mg/kg (Union Carbide 1980b). Histological examination of the pancreas, adrenal glands, pituitary, thyroid, or parathyroid revealed no lesions in rats at ≤ 885 mg/kg/day for 6 weeks, 5 days per week (Eastman Kodak 1983; Krasavage 1986) or in rats at ≥ 470 mg/kg/day and mice at $\leq 1,306$ mg/kg/day in drinking water for 13 weeks (NTP 1993). Likewise, in dermal studies, reddened adrenal glands, probably related to hemolysis, were seen in rabbits at ≥ 451 mg/kg for 6 hours (Union Carbide 1980a), but histological

2. HEALTH EFFECTS

examination of adrenals, pancreas, pituitary, thyroid, or parathyroid glands revealed no lesions in rabbits at ≤ 150 mg/kg/day 2-butoxyethanol 6 hours per day, 5 days per week for 90 days (CMA 1983).

Similarly, in studies on 2-butoxyethanol acetate, no gross or histologically observed lesions were noted in the pancreas or adrenal glands of rats and rabbits exposed by inhalation for 4 hours per day, 5 days per week to 400 ppm for 1 month, or to 100 ppm for 10 months in rats at an unspecified single gavage dose, or in rabbits at dermal doses $\leq 10,000$ mg/kg for 24 hours (Truhaut et al. 1979).

Since the only endocrine effects were hemorrhaged or reddened adrenal glands in animals exposed to high inhalation concentrations and high oral or dermal doses of 2-butoxyethanol, it is unlikely that humans exposed to 2-butoxyethanol or 2-butoxyethanol acetate in environmental, or hazardous waste site scenarios would experience endocrine effects.

Dermal Effects. No studies were located regarding dermal effects in humans after inhalation or oral exposure to 2-butoxyethanol, but dermal effects in humans after direct dermal exposure to neat 2-butoxyethanol included rigidity of the skin and decreased skin vohrme and skinfold thickness (Johanson et al. 1988). Slight erythema was noted during skin patch tests with 2-butoxyethanol acetate in humans (Jacobs et al. 1989), although a human sensitivity study in 201 persons with 10% 2-butoxyethanol showed no overt effect (CMA 1992; Greenspan et al. 1995). The 10% concentration was tested because it is the highest concentration found in cosmetics. Concentrations as high as 50% 2-butoxyethanol can be found in cleaning products which are intended to be diluted before use (OECD 1997).

In studies of 2-butoxyethanol in animals, dermal effects included necrosis of the tail tip in nonpregnant female rats at ≥ 250 ppm for up to 7 hours (Nelson et al. 1984) and in pregnant rats at 200 ppm for 6 hours per day during gestation (Tyl et al. 1984) in inhalation studies; in rats after a single oral dose of 1,000 mg/kg (Dow 1981); and in pregnant rats after dermal contact with 1.4 mL/day during gestation (Hardin et al. 1984). The cause of necrosis of the tail tip was not clearly stated, but possibly it is associated with the effects of 2-butoxyethanol on the red blood cells and subsequent vascular response.

In other oral studies of 2-butoxyethanol in animals, dermal effects consisted of rough coat in rats that died at ≥ 530 mg/kg (Carpenter et al. 1956), piloerection in rats at $>1,310$ mg/kg (Olin 1976), and pale coloration of the skin in rats at 600 mg/kg/day during gestation (NTP 1989). The rough coats and piloerection may be

2. HEALTH EFFECTS

related to neurotoxicity. Histological examination of skin revealed no dermal lesions in rats at ≤ 470 mg/kg/day or in mice at $\leq 1,306$ mg/kg/day (females) in drinking water for 13 weeks (NTP 1993).

In other dermal studies of 2-butoxyethanol in animals, dermal effects consisted of strong skin irritation in guinea pigs after application of unspecified doses (Eastman Kodak 1988); necrosis of epidermis and dermis in rabbits at ≥ 72 mg/kg for 8 hours (Duprat and Gradiski 1979); hyperemia, edema, slight exfoliation, and/or slight to moderate irritation in rabbits after dermal contact with undiluted or unspecified concentrations of 2-butoxyethanol (Dow 1958, 1959, 1981; Eastman Kodak 1988; Rohm and Haas 1983); necrosis and erythema in rabbits at ≥ 541 mg/kg for 6 hours (Union Carbide 1980a), at 902 mg/kg for 24 hours (Union Carbide 1980b), and at ≥ 18 mg/kg (for erythema) and ≥ 271 mg/kg (for necrosis) after nine applications (Union Carbide 1980a); slight to moderate erythema in rabbits at ≥ 10 mg/kg/day for 6 hours per day for 90 days (CMA 1983); and capillary congestion in rabbits after dermal contact with 0.01 mL of undiluted 2-butoxyethanol (Union Carbide 1980b).

The dermal irritation of 2-butoxyethanol and 2-butoxyethanol acetate have been studied in New Zealand rabbits using both the Draize protocol (24-hour occluded exposure) and the European Economic Communities protocol (4-hour occluded exposure) (Zissu 1995). For both protocols, 0.5 mL of undiluted compound was placed on the skin. 2-Butoxyethanol was considered a severe irritant by the Draize protocol, and an irritant by the European Economic Communities protocol. 2-Butoxyethanol acetate was considered a moderate irritant by the Draize protocol, and non-irritating by the European Economic Communities protocol.

In dermal studies of 2-butoxyethanol acetate in animals, mild to moderate erythema, indicating mild irritation, was observed in rabbits after dermal contact with undiluted 2-butoxyethanol acetate (Jacobs et al. 1989; Truhaut et al. 1979).

The data indicate that skin contact of humans with high concentrations of 2-butoxyethanol or 2-butoxyethanol acetate may result in skin irritation.

Ocular Effects. Eye irritation was experienced by humans exposed experimentally by inhalation to 2-butoxyethanol at ≥ 113 ppm for 4-8 hours (Carpenter et al. 1956), probably due to direct contact of the eyes with the 2-butoxyethanol vapor. A woman who ingested 391-469 mg/kg 2-butoxyethanol exhibited isocoric light reactive mydriasis (Gijzenbergh et al. 1989).

2. HEALTH EFFECTS

Ocular effects have been observed in animals after inhalation, oral, dermal, and ocular exposure to 2-butoxyethanol. Periocular wetness occurred during inhalation exposure of pregnant rats at ≥ 25 ppm and in pregnant rabbits at ≥ 100 ppm during gestation (Tyl et al. 1984). The periocular wetness was probably due to direct contact of the eyes with 2-butoxyethanol vapor. Slightly increased ocular secretions were observed in 2 dogs exposed to 415 ppm 2-butoxyethanol intermittently for 12 weeks (Werner et al. 1943b). A reddish ocular discharge accompanied by yellow discoloration of the sclera occurred in rabbits exposed to 400-411 ppm for 7 hours per day for 1-2 days (Dow 1986); these effects may have been secondary to the hemolytic property of 2-butoxyethanol. In other inhalation studies of 2-butoxyethanol in animals, ophthalmological examination revealed no effects in dogs exposed to 200 ppm for 31 days (Carpenter et al. 1956) or in rats exposed for 6 hours per day to ≤ 245 ppm for 9 days or to ≤ 77 ppm for 13 weeks (Dodd et al. 1983).

In oral studies of 2-butoxyethanol in animals, ocular effects consisted of palpebral closure in rats at 2,000 mg/kg (Dow 1981) and chromodacryorrhea in pregnant rats at 600 mg/kg/day during gestation (NTP 1989). However, histological examination of the eyes revealed no lesions in rats treated with ≤ 885 mg/kg/day by gavage for 6 weeks (Eastman Kodak 1983; Krasavage 1986), or in rats at ≤ 470 mg/kg/day, or mice at $\leq 1,306$ mg/kg/day in the drinking water for 13 weeks (NTP 1993).

In studies of 2-butoxyethanol instilled into the eyes of rabbits, severe irritation, moderate to extensive conjunctivitis, moderate corneal damage, and/or slight iritis were observed (Dow 1958, 1959, 1981; Kennah et al. 1989a; Rohm and Haas 1983; Union Carbide 1980b). In dermal studies, grey iris was observed in rabbits at 902 mg/kg for 6 hours (Union Carbide 1980a) or for 24 hours (Union Carbide 1980b); lacrimation at 2,000 mg/kg and a yellow cornea at 500 mg/kg occurred in rabbits (Olin 1976). For 2-butoxyethanol acetate, slight conjunctival redness and discharge were observed in rabbits after ocular instillation (Truhaut et al. 1979).

In a study designed to evaluate the use of *in vitro* cytotoxicity data for predicting the ocular irritancy potential of chemicals, BALB/c 3T3 cells were grown overnight, then exposed for 30 minutes to 10-100% (volume in culture) 2-butoxyethanol (Kennah et al. 1989b). Growth of the cells with 2-butoxyethanol compared to a control culture was recorded. The concentration at which the growth of the cells was inhibited by 50% compared to controls was calculated and compared to *in vivo* eye irritancy tests (Kennah et al. 1989a). A linear relationship was observed, although the *in vivo* tests indicated greater irritancy than would have been predicted from the cytotoxicity tests. Other *in vitro* test systems have been investigated using 2-butoxyethanol, with less than satisfactory results (Bagley et al. 1994; Booman et al. 1988).

2. HEALTH EFFECTS

The data indicate that exposure to vapors of 2-butoxyethanol or direct ocular contact with liquid 2-butoxy-ethanol would be irritating to the eyes of humans.

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation, oral, or dermal exposure to 2-butoxyethanol or 2-butoxyethanol acetate. However, effects on body weight have been observed in animals after inhalation, oral, and dermal exposure to 2-butoxyethanol or after oral exposure to 2-butoxyacetic acid.

In inhalation studies on 2-butoxyethanol in animals, weight loss, or decreased body weight gain was observed in rats at ≥ 523 ppm for 4 hours and at ≥ 83 ppm for 9 days (Dodd et al. 1983); in pregnant rats at 2 100 ppm and pregnant rabbits at 200 ppm for 6 hours per day during gestation (Tyl et al. 1984); in dogs at 385 ppm for 8 or 25 days (Carpenter et al. 1956); and in mice at 400 ppm for 60 days (Carpenter et al. 1956). Two dogs exposed to 415 ppm 2-butoxyethanol 17 hours per day 5 days per week for 12 weeks gradually lost 6-9% of their body weights (Werner et al. 1943b). No control body weight data were provided, although the study authors indicate that the other dogs in the study gained weight or remained constant throughout the study period.

In oral studies of 2-butoxyethanol in animals, weight loss, or reduced body weight gain was observed in rats at a gavage dose of 1,000 mg/kg/day for 4 days (Grant et al. 1985), at 885 mg/kg/day by gavage for 6 weeks (with decreased food consumption) (Eastman Kodak 1983; Krasavage 1983), at 265 mg/kg/day in drinking water for 2 weeks (with decreased water consumption), at 443 mg/kg/day in drinking water for 60 days (NTP 1993) (with decreased water consumption), and at ≥ 367 mg/kg/day for 13 weeks (with decreased water consumption in 1 of these studies) (Carpenter et al. 1956; NTP 1993), and in mice at 12,750 mg/kg/day in drinking water for 2 weeks (Heindel et al. 1990). In rats treated with 2-butoxyethanol in the diet for 91-93 days, body weight gain was decreased by 53% in males at 919 mg/kg/day and by 45% in females at 976 mg/kg/day (Weil and Carpenter 1963). Body weight gain was decreased by as much as 91% at day 1 of the study in males at 188 mg/kg/day but was only 9% lower than controls by the end of the study. The 188-mg/kg/day dose in males was also associated with about an 18% decrease in food intake. No effects on body weight gain were noted at 28 mg/kg/day in males and at 222 mg/kg/day in females. Pregnant rats exhibited decreased gestational weight gain (as well as decreased food and water intake) at ≥ 150 mg/kg/day during gestation (NTP 1989), as did pregnant mice at $\geq 1,000$ mg/kg/day during gestation (Hardin et al. 1987; Schuler et al. 1984; Wier et al. 1987) and at 1,300 mg/kg/day in drinking water (Heindel et al. 1990) in a reproductive study.

2. HEALTH EFFECTS

In dermal studies of 2-butoxyethanol, decreased body weight gain was observed in pregnant rats at 0.48 mL/day during gestation (Hardin et al. 1984) and in rats at 200 mg/kg for 24 hours (Dow 1959).

For 2-butoxyethanol acetate, no effect on body weight was noted in rats or rabbits exposed by inhalation intermittently to 400 ppm for 1 month or to 100 ppm for 10 months (Truhaut et al. 1979). For 2-butoxyacetic acid, rats given single gavage dose ≥ 174 mg/kg had decreased weight gain during the first 2 days after treatment at all doses, but the weight gain returned to normal by day 14 (Foster et al. 1987).

Effects on body weight do not appear to be a concern for humans exposed to 2-butoxyethanol, 2-butoxyethanol acetate, or 2-butoxyacetic acid in environmental or hazardous waste site scenarios.

Metabolic Effects. The only information regarding metabolic effects of 2-butoxyethanol comes from case reports of humans who ingested household cleaning agents containing 2-butoxyethanol. The metabolic effects consisted of metabolic acidosis and hypoxemia with lactic acidosis in the known alcohol and trichloroethylene abuser who ingested 650 mg/kg (Bauer et al. 1992), metabolic acidosis and hypokalemia in a patient who ingested 467-933 mg/kg (Rambourg-Schepens et al. 1988), and metabolic acidosis in another patient who ingested 391-469 mg/kg (Gijsenbergh et al. 1989). Significant acid-base disturbance was observed in a man following ingestion of 1,006-1,341 mg/kg 2-butoxyethanol in a concentrated glass cleaner (Gualtieri et al. 1995). A second ingestion of the glass cleaner (1,341 mg/kg 2-butoxyethanol) 12 days later did not result in metabolic disturbances. After the second ingestion, hemodialysis and ethanol treatment were initiated within 8 hours after exposure, but it is unclear how much time elapsed before treatment of first injection. It is to be expected that metabolism of significant quantities of 2-butoxyethanol to 2-butoxyacetic acid would cause metabolic acidosis.

Whether or not humans exposed to 2-butoxyethanol in environmental or hazardous waste site scenarios would have metabolic effects cannot be determined based on the limited available data.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation, oral, or dermal exposure to 2-butoxyethanol. In animal studies on 2-butoxyethanol, other systemic effects consisted of reduced food consumption at ≥ 100 ppm and reduced water consumption at 200 ppm in pregnant rats exposed to 2-butoxyethanol vapors for 6 hours per day during gestation (Tyl et al. 1984); decreased water consumption in rats at ≥ 152 mg/kg/day and in mice at ≥ 150 mg/kg/day in drinking water for 2 weeks (Heindel et al. 1990; NTP 1993); dehydration in mice at ≥ 376 mg/kg/day in drinking water for 2 weeks (NTP 1993);

2. HEALTH EFFECTS

decreased food and water intake at ≥ 150 mg/kg/day, and coldness to the touch at 600 mg/kg/day in pregnant rats given gavage doses during gestation (NTP 1989); decreased water consumption in rats at ≥ 444 mg/kg/day in drinking water for 21 days (Exon et al. 1991); decreased food consumption in rats at 885 mg/kg/day by gavage for 6 weeks (Eastman Kodak 1983; Krasavage 1986); decreased water consumption in rats at ≥ 128 mg/kg/day in drinking water for 13 weeks (NTP 1993); decreased food intake in rats fed 2-butoxyethanol in the diet at ≥ 188 mg/kg/day for males and 976 mg/kg/day for females (Weil and Carpenter 1963); and decreased water consumption in mice at 700 mg/kg/day in drinking water for up to 25 weeks (Heindel et al. 1990).

Although decreased food and water consumption may have been due to unpalatability of 2-butoxyethanol in the dietary and drinking water studies, these effects were also observed in animals after inhalation or gavage treatment. Furthermore, the decreased body weight gain observed in animals in some studies cannot be completely attributed to decreased food or water intake. Nevertheless, decreased water consumption and decreased food intake do not appear to be effects of concern in humans exposed to 2-butoxyethanol under any scenario.

Immunological and Lymphoreticular Effects. No studies were located regarding immunological and lymphoreticular effects in humans after inhalation or oral exposure to 2-butoxyethanol or 2-butoxyethanol acetate. Slight erythema, but no allergic reaction, was noted on skin-patch tests with 2-butoxyethanol acetate in humans (Jacobs et al. 1989). A human sensitivity study in 201 individuals with 10% 2-butoxyethanol showed no overt effect (CMA 1992; Greenspan et al. 1995). The 10% concentration was tested because it is the highest concentration found in cosmetics. Concentrations as high as 50% 2-butoxyethanol can be found in cleaning products which are intended to be diluted before use (OECD 1997).

The information on immunological effects of 2-butoxyethanol in animals consists of the following findings: no effect on the immune system was found in rats at gavage doses of ≤ 400 mg/kg/day for 2 days following immunization with trinitrophenyl-lipopolysaccharide (TNP-EPS) (Smialowicz et al. 1992); and no IgG change compared with controls in antibody production or delayed-type hypersensitivity response after-challenge with anti-keyhole limpet hemocyanin; also, no adverse effects on natural killer cell function or splenocyte production of cytokines, or thymus and spleen weights were observed. No effect on thymus or spleen weight, and no histopathological lesions in the thymus were observed in rats given ≤ 506 mg/kg/day for 21 days (Exon et al. 1991). 2-Butoxyethanol has also tested negative for dermal sensitization in guinea pigs using the maximized Magnusson and Kliman test (Zissu 1995).

2. HEALTH EFFECTS

Several studies in animals describe effects on the spleen, all of which are probably related to the hematological effect of 2-butoxyethanol and the resultant accumulation of lysed red blood cells in the spleen.

In inhalation studies on 2-butoxyethanol in animals, splenic effects consisted of increased spleen weight in pregnant rats at 200 ppm for 6 hours per day during gestation (Tyl et al. 1984). However, histological examination of the spleen, mediastinal lymph nodes, and thymus revealed no lesions in rats exposed intermittently to ≤ 177 ppm for 13 weeks (Dodd et al. 1983).

In oral studies on 2-butoxyethanol in animals, effects on lymphoreticular organs consisted of increased spleen weight in pregnant rats at ≤ 100 mg/kg/day during gestation (NTP 1989), in young and adult rats at ≥ 125 mg/kg by gavage (Ghanayem et al. 1987a, 1987b) or 125 mg/kg/day for up to 12 days (Ghanayem et al. 1992), and increased spleen weight accompanied by extramedullary hematopoiesis at ≥ 500 mg/kg/day for 4 days (Grant et al. 1985). In addition, splenic congestion, secondary to hematological effects, at ≥ 222 mg/kg/day and increased spleen weight and enlarged dark spleens at ≥ 443 mg/kg/day were observed in rats treated by gavage for 6 weeks, but no histological lesions were seen in any lymphoreticular organs (Eastman Kodak 1983; Krasavage 1986). Decreased thymus weight occurred in mice at ≥ 370 mg/kg/day in drinking water for 2 weeks (NTP 1993). Bone marrow hyperplasia at ≥ 281 mg/kg/day, hematopoietic cell proliferation at ≥ 363 mg/kg/day, increased hemosiderin pigmentation in the spleen at ≥ 129 mg/kg/day, and decreased thymus weight at ≥ 367 mg/kg/day were found in rats given 2-butoxyethanol in drinking water for 13 weeks (NTP 1993). None of these effects occurred in mice similarly exposed at $\leq 1,306$ mg/kg/day.

In dermal studies on 2-butoxyethanol in animals, effects on lymphoreticular organs consisted of congestion in the spleen, erythrocytic infiltration, and white atrophic pulp in rabbits at ≥ 72 mg/kg/day for 8 hours (Duprat and Gradiski 1979); engorged spleen in rabbits at ≥ 406 mg/kg (Carpenter et al. 1956); and enlarged spleen in rabbits at 902 mg/kg for 6 hours (Union Carbide 1980a) and dark red spleens at ≥ 451 mg/kg for a 24-hour exposure (Union Carbide 1980b).

For 2-butoxyethanol acetate, no gross or histopathological lesions were found in the spleen of rats or rabbits exposed by inhalation intermittently to 400 ppm for 1 month or to 100 ppm for 10 months, in rats at unspecified single gavage doses, or in rabbits exposed dermally at $\leq 10,000$ mg/kg for 24 hours (Truhaut et al. 1979).

2. HEALTH EFFECTS

The limited available data in humans and animals indicate that exposure to 2-butoxyethanol or 2-butoxy-ethanol acetate under any scenario would not result in immunological effects; however, lymphoreticular effects in the spleen and bone marrow, which are probably attributable to the hemolytic effects of 2-butoxyethanol, may occur in humans exposed to high levels of 2-butoxyethanol.

Neurological Effects. Humans exposed experimentally by inhalation to 2-butoxyethanol for 4-8 hours experienced headache at 98 ppm and disturbed taste sensation at 113 and 195 ppm (Carpenter et al. 1956). Case reports of intentional poisoning indicate that coma can result from the ingestion of ≥ 467 mg/kg 2-butoxyethanol (Bauer et al. 1992; Gijzenbergh et al. 1989; Litovitz et al. 1991; Rambourg-Schepens et al. 1988).

Neurological effects have been observed in animals after inhalation, oral, and dermal exposure to 2-butoxyethanol. In inhalation studies of 2-butoxyethanol in animals, neurological effects consisted of loss of coordination in rats at ≥ 523 ppm for 4 hours (Dodd et al. 1983), extreme weakness in dogs at 617 ppm for 2 days, weakness and apathy in dogs at 385 ppm for 8 or 28 days (Carpenter et al. 1956), excessive salivation in dogs at 400 ppm for 5 days (Dow 1972, 1986), and poor coordination of the extremities and loss of equilibrium in rabbits at 400 ppm 2-butoxyethanol for 7 hours per day on 1-2 days (Dow 1986).

In oral studies of 2-butoxyethanol in animals, neurological effects consisted of sluggishness, prostration, and narcosis in rats that died after gavage doses ≥ 530 mg/kg (Carpenter et al. 1956) and drowsiness, sluggishness, lethargy, muscle flaccidity, and/or ataxia in rats at 252-9,000 mg/kg/day (Dow 1959, 1981; Eastman Kodak 1983; Krasavage 1986; Olin 1976; Union Carbide 1980b). Ataxia was reported in rats following a single gavage dose of 500 mg/kg (Sivarao and Mehendale 1995). Moderate to severe weakness and prostration was observed directly after dosing in guinea pigs given a single gavage dose of 1,000 mg/kg 2-butoxyethanol, a dose that resulted in the death of one of five males, and one of five females (Shepard 1994b). Slight weakness was observed directly after dosing at 500 mg/kg, a dose at which all treated guinea pigs survived. Lethargy also was observed in pregnant rats treated at 600 mg/kg/day by gavage during gestation (NTP 1989) and in rats at ≥ 443 mg/kg/day for 6 weeks (Eastman Kodak 1983; Krasavage 1986), and lethargy and failure to right were observed in pregnant mice treated at $\geq 1,500$ mg/kg/day by gavage during gestation (Wier et al. 1987).

In dermal studies of 2-butoxyethanol in animals, neurological effects consisted of prostration and narcosis prior to death in rabbits at ≥ 72 mg/kg for 8 hours (Duprat and Gradiski 1979); muscle flaccidity at 1,000 and 2,000 mg/kg and anorexia and no spontaneous movement at 2,000 mg/kg prior to death in rabbits treated with

2. HEALTH EFFECTS

2-butoxyethanol for 24 hours on abraded skin (Olin 1976); ataxia progressing to moderate-to-marked inactivity prior to death in pregnant rats at 1.4 mL/day during gestation (Hardin et al. 1984); and nystagmus and convulsion prior to death in rabbits at 902 mg/kg (Union Carbide 1980a).

For 2-butoxyethanol acetate, no clinical signs of neurotoxicity and no histopathological lesions in the brain were found in rats or rabbits exposed by inhalation intermittently to 400 ppm for 1 month or to 100 ppm for 10 months, in rats at unspecified single gavage doses, or in rabbits exposed dermally at $\leq 10,000$ mg/kg for 24 hours (Truhaut et al. 1979).

The data indicate that humans exposed to sufficient quantities of 2-butoxyethanol by any route may experience lethargy, but more serious neurological effects would not be expected to occur in humans exposed to 2-butoxyethanol or 2-butoxyethanol acetate under environmental or hazardous waste site scenarios.

Reproductive Effects. No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to 2-butoxyethanol or 2-butoxyethanol acetate.

Reproductive effects have been observed in animals after inhalation, oral, and dermal exposure to 2-butoxyethanol. In inhalation studies, reproductive effects consisted of reduced maternal gravid uterine weight, decreased percentages of viable implants and in live fetuses per litter, and an increase in non-viable implants in pregnant rats, and decreased total implants and implant viability in pregnant rabbits at 200 ppm during gestation (Tyl et al. 1984). This concentration also resulted in the death of 4 of 24 exposed rabbits, and maternal hematological effects.

In oral studies on 2-butoxyethanol in animals, reproductive effects consisted of decreased sperm concentration (with no effects on spermatid heads, spermatid counts, or percent mobile sperm) in male rats at ≥ 281 mg/kg/day in drinking water for 13 weeks (NTP 1993); testicular atrophy and decreased body weight gain were observed in rats fed 2-butoxyethanol in the diet at 188 mg/kg/day for about 90 days (Weil and Carpenter 1963); altered estrous cycles (more time spent in diestrus) with no change in total cycle length in female rats at ≥ 363 mg/kg/day in the drinking water for 13 weeks (NTP 1993); vaginal bleeding at 200-600 mg/kg/day and increased resorptions and implantation loss at ≥ 200 mg/kg/day in rats during gestation (NTP 1989); decreased incidence of viable litters in pregnant mice at 1,180 mg/kg/day by gavage during gestation (Hardin et al. 1987; Schuler et al. 1984); a green or red vaginal discharge at $\geq 1,500$ mg/kg/day and increased resorptions at $\geq 1,000$ mg/kg/day in mice during gestation (Wier et al. 1987);

2. HEALTH EFFECTS

and a decrease in the number of litters produced per breeding pair and litter size in mating pairs of mice at $\geq 1,300$ mg/kg/day in drinking water for 21 weeks (Heindel et al. 1990). Cross-breeding experiments indicated that these effects were due to effects on the females (Heindel et al. 1990).

In dermal studies on 2-butoxyethanol in animals, the only reproductive effect consisted of a slight increase in testicular weight of male rabbits at 150 mg/kg/day for 6 hours per day for 90 days (CMA 1983). Histological examination of reproductive organs of males and females revealed no lesions.

For 2-butoxyethanol acetate, no histopathological lesions were found in testes or ovaries in rats or rabbits exposed by inhalation intermittently to 400 ppm for 1 month or to 100 ppm for 10 months, in rats exposed orally at unspecified single gavage doses, or in rabbits exposed dermally to $\leq 10,000$ mg/kg for 24 hours (Truhaut et al. 1979).

The data indicate that reproductive effects might be a concern for pregnant women exposed to high levels of 2-butoxyethanol. Based on the findings in male animals, little concern is indicated for reproductive effects in men.

Developmental Effects. No studies were located regarding developmental effects in humans after inhalation, oral, or dermal exposure to 2-butoxyethanol or 2-butoxyethanol acetate. No studies were located regarding developmental effects in animals after exposure to 2-butoxyethanol acetate by any route. However, developmental effects have been observed in animals after inhalation, oral, and dermal exposure to 2-butoxyethanol.

In inhalation studies on 2-butoxyethanol in animals, the developmental effects consisted of retarded skeletal ossification in the offspring of pregnant rats at ≥ 100 ppm and in pregnant rabbits at 200 ppm for 6 hours per day during gestation (Tyl et al. 1984). In oral studies, the developmental effects consisted of decreased fetal body weight of the offspring of pregnant rats at ≥ 300 mg/kg/day and decreased gravid uterine weight of rat dams at 600 mg/kg/day during gestation (NTP 1989), and some evidence of cleft palate in the fetuses of pregnant mice given $\geq 1,000$ mg/kg/day during gestation (Wier et al. 1987). In a reproductive toxicity study in male and female mice, decreased pup weight was observed in all mating pairs at ≥ 700 mg/kg/day in drinking water for 21 weeks (Heindel et al. 1990). A crossover mating trial indicated that the reproductive effects could be attributed primarily to an effect on the female. In dermal studies on 2-butoxyethanol, no developmental effects were observed in the offspring of pregnant rats at 0.48 mL/day during gestation (Hardin et al. 1984).

2. HEALTH EFFECTS

With the exception of decreased pup weight observed in mice at 700 mg/kg/day (Heindel et al. 1990), developmental effects reported occurred at 2-butoxyethanol doses that resulted in moderate to severe maternal toxicity (Hardin et al. 1987; NTP 1989; Tyl et al. 1984; Wier et al. 1987).

2-Butoxyethanol has been shown to have developmental toxicity in an *in vitro* assay using the fresh water coelenterate *Hydra attenuata* (Bowden et al. 1995; Johnson et al. 1984), whereas both 2-butoxyethanol (Bowden et al. 1995; Giavini et al. 1993) and 2-butoxyacetic acid (Giavini et al. 1993; Rawlings et al. 1985) have been shown to be embryotoxic in rat embryo culture. A significant increase in malformations (anomalous encephalon, hypoplasia of the branchial arches, unrotated) was observed only at the highest concentration of 2-butoxyethanol (12.5 mM) used in this study, but not at 6.25 mM (Giavini et al. 1993). Malformations noted following exposure to 2-butoxyacetic acid at concentrations of 0.8 mM and greater were anomalous encephalon and irregular disposition of the somites (Giavini et al. 1993); however, another study found abnormalities at 5 mM 2-butoxyacetic acid (no statistics done), but not at 2 mM (Rawlings et al. 1985). Based on the *in vitro* data, Bowden et al. (1995) suggested that 2-butoxyethanol “presents a teratogenic potential that *in vivo* is masked by maternal toxicity.”

The available data indicate that low birth weights and delayed ossification might be concerns for the offspring of pregnant women exposed to high levels of 2-butoxyethanol.

Genotoxic Effects. No increases in micronuclei or sister chromatid exchanges were observed in varnish production workers exposed to both 2-ethoxyethanol and 2-butoxyethanol (Sohnlein et al. 1993). Postshift biological monitoring for the acetic acids in urine indicated that urinary levels of 2-ethoxyacetic acid (53.8 mg/L) were higher than urinary levels of 2-butoxyacetic acid (16.4 mg/L). One report of a 2-butoxyethanol test in a rat primary hepatocyte test was located (McGregor 1984). [¹⁴C]2-Butoxyethanol was tested for 2 hours at concentrations up to 0.1% in the culture medium. Significant increases in nuclear and DNA-associated radioactivity at two low-dose levels were observed, with the maximum response 1.3 times the control levels. 2-Butoxyethanol was reported not to induce sister chromatid exchange in Chinese hamster ovary cells exposed to concentrations up to 0.25% for 2 hours in the presence of metabolizing enzymes (S9) and for 5 hours in the absence of S9 (Tyler 1982). 2-Butoxyethanol and 2-butoxyacetic acid did not result in mutagenic effects in Chinese hamster ovary cells exposed for 5 hours (Chiewchanwit and Au 1995). The maximum non-toxic concentrations studied were 1% for 2-butoxyethanol and 6.5% for 2-butoxyacetic acid.

2. HEALTH EFFECTS

The mutagenic effect of 2-butoxyethanol was investigated using bacteriophage T4D with *Escherichia coli* B, CR63, and K12 (Kvelland 1988). No mutagenic activity was observed, but 2-butoxyethanol had a severe toxic effect on phage yield. 2-Butoxyethanol was negative for mutation in *Salmonella typhimurium* strains TA98, TA100, and TA102 both with and without rat S-9 activation (Hoflack et al. 1995). In *S. typhimurium* strain TA97a, 2-butoxyethanol tested positive for mutation both with and without S-9 activation. The mutation assay of 2-butoxyethanol in strain TA97a was repeated by Gollapudi et al. (1996). In this study, 2-butoxyethanol was negative for mutations both with and without rat S-9 metabolic activation, and it was negative in *E. coli* WP2uvrA strain. Gollapudi et al. (1996) suggested that Hoflack et al. (1995) found positive results because they used 2-butoxyethanol contaminated with higher levels of peroxides, which test positive in strain TA97a. The 2-butoxyethanol used by Gollapudi et al. (1996) contained 23 ppm of peroxides which was measured just before the tests. The 2-butoxyethanol used by Hoflack et al. (1995) contained less than 50 ppm peroxides according to the manufacturer, but the actual concentrations of peroxides may have been higher since measurements were not made immediately prior to testing. Gollapudi et al. (1996) concluded that peroxides and/or experimental variables probably account for the difference in results observed in their study and in the study by Hoflack et al. (1995). *In vitro* genotoxic effects are shown in Table 2-13.

Cancer. No studies were located regarding carcinogenic effects in humans or animals after exposure to 2-butoxyethanol, 2-butoxyethanol acetate, or 2-butoxyacetic acid by any route. However, structure-activity studies with 2-butoxyethanol and eight other glycol ethers were conducted with a cellular leukemia transplant model in male Fischer 344 rats to determine the chemotherapeutic potential of these glycol ethers (Dieter et al. 1990). 2-Butoxyethanol was administered *ad libitum* in the drinking water to male rats at doses of 0, 3, or 6 mg/mL. Treatment was begun after the rats were injected with the leukemic transplant. Untreated transplant control rats and untreated non-transplant controls were also included. Treatment continued for 55-65 days, at which time the animals were killed and blood was analyzed. 2-Butoxyethanol had no effect on the progression of the leukemic transplant.

2-Butoxyethanol and 2-butoxyethanol acetate have not been classified for carcinogenic effects by the Department of Health and Human Services (DHHS), the National Toxicology Program (NTP), the International Agency for Research on Cancer (IARC), or EPA.

Table 2-13. Genotoxicity of 2-Butoxyethanol *In Vitro*

Species (test system)	End point	Result		Reference
		With activation	Without activation	
Prokaryotic organisms				
<i>Escherichia coli</i> (T4D phage)	Mutagenesis	-	-	Kvelland 1988
CR63 (T4D phage)	Mutagenesis	-	-	Kvelland 1988
K12 (T4D phage)	Mutagenesis	-	-	Kvelland 1988
<i>Salmonella typhimurium</i> TA98, TA100, TA102	Mutagenesis	-	-	Hoflack et al. 1995
<i>S. typhimurium</i> TA97a	Mutagenesis	+	+	Hoflack et al. 1995
<i>S. typhimurium</i> TA97a, TA100	Mutagenesis	-	-	Gollapudi et al. 1996
<i>E. coli</i> WP2 <i>ovr</i>	Mutagenesis	-	-	Gollapudi et al. 1996
Mammalian cells				
Rat (primary hepatocyte)	DNA-associated radioactivity	No data	+	McGregor 1984
Chinese hamster (ovary cells)	Sister chromatid exchange	-	-	Tyler 1982
Chinese hamster (ovary cells)	Mutagenesis	No data	-	

- = negative results; + = positive results

2. HEALTH EFFECTS

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAWNRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 2-butoxyethanol and 2-butoxyethanol acetate are discussed in Section 2.6.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NASKNRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 2-butoxyethanol and 2-butoxyethanol acetate are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically

2. HEALTH EFFECTS

effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed -in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to 2-butoxyethanol

The presence of 2-butoxyacetic acid in the urine is the accepted biomarker of exposure for both 2-butoxyethanol and 2-butoxyethanol acetate (Johanson et al. 1989) and has been used in surveys of occupational exposure, although 2-butoxyethanol has also been detected in blood and urine (Angerer et al. 1990; Haufroid et al. 1997; Johanson 1988; Johanson and Boman 1991; Johanson and Femstrom 1986; Johanson and Johnsson 1991; Johanson et al. 1986a, 1988, 1989; Jiinsson and Steen 1978; Rettenmeier et al. 1993; Sakai et al. 1994; Vincent et al. 1993). These have also been used as biomarkers of exposure in animal experiments (Ghanayem et al. 1987a, 1987b, 1987c, 1992; Medinsky et al. 1990; Romer et al. 1985; Sabourin et al. 1992a, 1992b, 1993). More recently, analytical methods have been able to detect 2-butoxyacetic acid in human blood (Johanson and Johnsson 1991). Urinalysis for 2-butoxyacetic acid should include detection of glutamine conjugates since the amount of conjugate detected in urine can be equal to or greater than the amount of free 2-butoxyacetic acid (Rettenmeier et al. 1993; Sakai et al. 1994)

For practical purposes, estimates of exposure can best be made from 2-butoxyacetic acid levels in the urine. Based on the work of Johanson (1988), 2-butoxyacetic acid is the appropriate biomarker of exposure for the following reasons: it is not normally in human urine, it can be reliably assayed with current methods, levels in the urine are not affected by hemolytic activity, the elimination half-life (4-7 hours) reflects exposure over the workday, and urine collection is non-invasive. Possible sources of variation and error inherent in the biological monitoring of 2-butoxyacetic acid in the urine include variable uptake during inhalation exposure caused by changes in workload, or during dermal exposure caused by changes in temperature and humidity, and changes in excretion caused by alcohol consumption or other personal habits (e.g., smoking) (Johanson and Boman 1991; Johanson et al. 1988). Inter-individual variation in the rates of absorption, distribution, metabolism, and excretion may also influence the evaluation of 2-butoxyacetic acid in the urine of exposed individuals. For example, a genetic polymorphism in the CYP 2E1 gene may possibly result in differences in the metabolism of 2-butoxyethanol; this speculation is based on the results of one study in which urinary levels of free butoxyacetic acid (conjugates were not measured) were measured in 30 c1/c1 homozygotes and one c1/c2 heterozygote (Haufroid et al. 1997). Persons heterozygous for the c2 allele may produce less 2-butoxyacetic acid, and more ethylene glycol than persons homozygous for the c1 allele; however, ethylene glycol and its metabolites were not measured in the urine in this study. This hypothesis merits further

2. HEALTH EFFECTS

investigation. Studies indicate that the concentration of 2-butoxyacetic acid in the urine may not be linearly correlated with the absorbed dose; however, for individuals, it is related to absorbed dose and thus is a useful measure (Johanson 1988; Johanson et al. 1986a). Since these studies examined only free 2-butoxyacetic acid, it is unknown how much conjugated 2-butoxyacetic acid was in the urine. Because some (15-27% worst case) dermal absorption may occur from vapor exposure, 2-butoxyacetic acid in the urine resulting from ambient air concentrations of 2-butoxyethanol may represent both pulmonary and dermal absorption (Corley et al. 1997; Johanson and Boman 1991). Individual monitoring throughout the work day (urine samples prior to and after the workshift) may be a good choice for widescale biological monitoring in the occupational setting.

2-Butoxyethanol has been shown to increase human plasma osmolality *in vitro* (Browning and Curry 1992). The osmolal gap is frequently used in the evaluation of a patient who has accidentally or intentionally ingested a glycol ether or related compound (Gijzenbergh et al. 1989). The presence of an elevated osmolal gap indicates the presence of significant blood levels of the toxic compound. This is not an indicator that is specific to 2-butoxyethanol or 2-butoxyethanol acetate and should be used in conjunction with other biomarker assays.

2.6.2 Biomarkers Used to Characterize Effects Caused by 2-Butoxyethanol

Hematotoxic effects are the characteristic biomarker of effect for 2-butoxyethanol exposure of animals (Bartnik et al. 1987; Ghanayem et al. 1987a, 1987b). In animals 2-butoxyethanol-induced hemolytic anemia is accompanied by a dose- and time-dependent decrease in the number of circulating red blood cells and decreases in hemoglobin concentration and hematocrit (Ghanayem et al. 1987a, 1987b). Hemolysis has been shown to be preceded by erythrocyte swelling (Ghanayem et al. 1989). Thus, hematological evaluations could be useful in monitoring effects of 2-butoxyethanol exposure. Work by Ghanayem et al. (1990b) indicates that using an impedance-based hematology analyzer allows for the detection of the erythrocytic swelling early after exposure that is undetectable by laser-based analyzer. Both analyzers were able to detect the subsequent decrease in red blood cell concentration signaling hemolytic effects (Ghanayem et al. 1990b). Thus, routine hematology using an appropriate hematology analyzer could be useful in detecting early hemolytic effects after 2-butoxyethanol exposure.

2-Butoxyethanol has been shown to increase human plasma osmolality *in vitro* (Browning and Curry 1992). The osmolal gap is frequently used in the evaluation of a patient who has accidentally or intentionally ingested a glycol ether or related compound (Gijzenbergh et al. 1989). The presence of an elevated osmolal gap is

2. HEALTH EFFECTS

associated with metabolic acidosis, which has been observed in humans after ingestion of 2-butoxyethanol (Bauer et al. 1992; Gijzenbergh et al. 1989; Rambourg-Schepens et al. 1988). This is not an indicator that is specific to 2-butoxyethanol or 2-butoxyethanol acetate and should be used in conjunction with other biomarker assays.

The use of urinary D-glucaric acid as a biomarker of effect following exposure to 2-butoxyethanol has been examined in 12 or 13 foundry workers exposed to the compound in paints and 18 unexposed controls (Collinot et al. 1996). Increased urinary D-glucaric acid is a nonspecific indicator of an increase in the activity of the glucuronic acid enzyme pathway. Urinary levels of D-glucaric acid were measured both in the summer and winter, and exposure concentrations were measured only in winter when they were expected to be higher because of reduced ventilation. Urinary concentrations of D-glucaric acid in nmol/hour were $2,095 \pm 991$ in controls, $3,888 \pm 2,284$ in the exposed workers during summer, and $5,792 \pm 2,387$ in the exposed workers during winter. The values were significantly different from controls at levels of $p < 0.05$ during summer and $p < 0.01$ during winter. When the groups were divided into smokers and nonsmokers, the smokers showed a higher level of D-glucaric acid than the nonsmokers. The exposure concentrations never exceeded 7.5 ppm, and the study authors indicated that other substances were undetectable (detection limits not stated). Although measurement of D-glucaric acid is not an effect specific to 2-butoxyethanol exposure, the study authors concluded that it was more sensitive than a standard blood count.

2.7 INTERACTIONS WITH OTHER CHEMICALS

Data describing the interaction of 2-butoxyethanol or 2-butoxyethanol acetate with other chemicals are scarce. Simulations of human pharmacokinetics of co-exposure to ethanol (0.1% in the blood) during an 8-hour exposure to 20 ppm 2-butoxyethanol with no exercise predict that the arterial levels of 2-butoxyethanol will be elevated as a result of a decrease in elimination rate (Johanson 1986, 1991a; Johanson and Naslund 1988). Because the increase in 2-butoxyethanol is due to decreased elimination and not increased uptake, the rise and fall of blood concentrations of 2-butoxyethanol are slower in the ethanol co-administration model than in the increased workload model. A study in rats indicated that co-administration of ethanol and 2-butoxyethanol resulted in a higher blood level and a prolonged blood elimination time of 2-butoxyethanol than administration of 2-butoxyethanol alone (Romer et al. 1985). The prolonged retention of 2-butoxyethanol was considered to be due to inhibition of metabolism of 2-butoxyethanol to 2-butoxyacetaldehyde via competition with ethanol for alcohol dehydrogenase, the enzyme common to the metabolism of both ethanol and 2-butoxyethanol. Based on these results in rats, the study authors concluded that the elimination of 2-butoxyethanol could be

2. HEALTH EFFECTS

inhibited in humans after consumption of alcoholic beverages and simultaneous exposure to 2-butoxyethanol. As discussed in Section 2.9.3, administration of ethanol after 2-butoxyethanol exposure can be used to control the production of toxic metabolites and to promote conjugation of the parent compound to nontoxic products of elimination such as the glucuronide and sulfate conjugates of 2-butoxyethanol.

Hemolysis is a critical effect of exposure to 2-butoxyethanol, but it is unknown whether 2-butoxyethanol interacts with other hemolytic agents, such as naphthalene, the toxicity of which is reviewed in the ATSDR *Toxicological Profile for Naphthalene* (ATSDR 1995b).

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 2-butoxyethanol than will most persons exposed to the same level of 2-butoxyethanol in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., alcohol and cigarette smoke). These parameters may result in reduced detoxification or excretion of 2-butoxyethanol, or compromised function of target organs affected by 2-butoxyethanol. Populations who are at greater risk due to their unusually high exposure to 2-butoxyethanol are discussed in Section 5.6, Populations With Potentially High Exposure.

Since the hemolytic effect of 2-butoxyethanol is caused by the action of the toxic metabolite 2-butoxyacetic acid, presumably on the red cell membrane, populations that are unusually susceptible to the toxic effects of 2-butoxyethanol would be those that have increased metabolism to 2-butoxyacetic acid and decreased excretion of 2-butoxyacetic acid. Persons whose red blood cell walls are less resistant to the effects of 2-butoxyacetic acid would also be more sensitive to 2-butoxyethanol. However, erythrocytes from normal, aged, sickle-cell anemia, and hereditary spherocytosis patients were resistant to the hemolytic effects of 2-butoxyacetic acid *in vitro* (Udden 1996; Udden and Patton 1994). Since erythrocytic swelling has been shown to precede hemolysis in rats after 2-butoxyethanol exposure, Udden and Patton (1994) investigated the possibility that increased deformability of erythrocytes in humans could predispose the individual to 2-butoxyethanol toxicity. They exposed erythrocytes from normal, aged, sickle-cell anemia, and hereditary spherocytosis patients to 2-butoxyacetic acid, the hemolytic metabolite of 2-butoxyethanol, *in vitro* under conditions that cause hemolysis of rat erythrocytes. No increase in hemolysis, changes in mean cellular volume or morphology, or deformability were found in any of the human erythrocytes. However, further definition of the metabolic or structural differences that render human erythrocytes more resistant to the effects of 2-butoxy-

2. HEALTH EFFECTS

ethanol compared to rat erythrocytes may also point to characteristics in the human population that may indicate increased susceptibility. It is unknown whether people with a genetic predisposition to hemolytic anemia from other causes (such as glucose-6-phosphate dehydrogenase mutations) will be more susceptible to 2-butoxyethanol-induced hemolysis.

In rats, Ghanayem et al. (1987a, 1990a) have shown that susceptibility to the hematotoxic effects of 2-butoxyethanol increases with increasing age. Investigation of the respiratory excretion and urinary metabolites of young (4-5 weeks old) and adult (9-13 weeks old) rats indicated that adult rats excreted a significantly lower proportion of the administered dose as respiratory CO₂ and eliminated less in the urine as the 2-butoxyethanol-glucuronide; more was eliminated as 2-butoxyacetic acid. No studies of this kind have been done in humans. However, it is possible that people of advanced age or with altered hepatic conjugating enzymes, reduced respiratory capacity, or compromised renal status could be at greater risk for toxic reactions to 2-butoxyethanol exposure.

Some incomplete and very tentative results on the influence of a CYP2E1 Polymorphism on the metabolism of 2-butoxyethanol are discussed in Section 2.3.3 Metabolism.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 2-butoxyethanol. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 2-butoxyethanol. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following text provides specific information about treatment following exposures to 2-butoxyethanol: Ellenhorn and Barceloux 1988.

2.9.1 Reducing Peak Absorption Following Exposure

Human exposure to 2-butoxyethanol or 2-butoxyethanol acetate can occur by inhalation, oral, or dermal contact. General recommendations for reducing absorption of 2-butoxyethanol or 2-butoxyethanol acetate following acute high-level inhalation exposure have included moving the patient to fresh air and monitoring for respiratory distress (Ellenhorn and Barceloux 1988); washing exposed skin after high level air exposure is probably a good idea since there can be some dermal absorption from 2-butoxyethanol vapors as well (Corley

2. HEALTH EFFECTS

et al. 1997). In the case of eye exposure, irrigation with copious amounts of water or saline have been recommended (Ellenhorn and Barceloux 1988). The removal of contaminated clothing and a thorough washing of exposed areas with soap and water have also been recommended (Ellenhorn and Barceloux 1988). Induction of emesis may be indicated following recent substantial ingestion of 2-butoxyethanol or 2-butoxyethanol acetate unless the patient is or could rapidly become comatose or convulsive (Ellenhorn and Barceloux 1988). Furthermore, the use of emetics may result in aspiration pneumonitis. Gastric lavage has been recommended, but charcoal and cathartics may be ineffective (Ellenhorn and Barceloux 1988). Gastric lavage and induced emesis using syrup of ipecac have been used in the treatment of accidental poisoning of children (Dean and Krenzelok 1992).

2.9.2 Reducing Body Burden

As discussed in Section 2.3 on Toxicokinetics, following absorption into the blood, 2-butoxyethanol is rapidly distributed throughout the body. Since 2-butoxyethanol is slightly hydrophilic, it is not preferentially distributed to lipid-rich tissues. 2-Butoxyethanol toxicity results from the formation of 2-butoxyacetic acid in the liver, through alcohol dehydrogenases. Dealkylation to ethylene glycol may also account for some toxicity. Detoxification pathways generally involve the formation of the sulfate and glucuronide conjugates of the parent compound and conjugation and excretion of the active metabolite 2-butoxyacetic acid. Exhalation is a minor route for excretion of CO₂ from 2-butoxyacetic acid and ethylene glycol, but metabolites are primarily excreted in the urine. Studies in humans and animals indicate that both exhalation and urinary excretion occur in several phases, with half-lives of minutes to hours. Hence, 2-butoxyethanol and its metabolites have relatively short half-lives in the body, and while some of these metabolites are toxic, substantial body burdens are not expected.

It is possible that methods could be developed to enhance detoxification and elimination pathways for the parent compound, in preference to oxidation pathways leading to 2-butoxyacetic acid, to aid in ridding the body of what has been absorbed prior to the production of toxic metabolites.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

The toxicity of 2-butoxyethanol has been shown to be dependent on the production of 2-butoxyacetic acid via alcohol dehydrogenases through the metabolic intermediate butoxyacetaldehyde. Methods successful in interfering with the mechanism of action for toxic effects are those that interfere with the metabolic

2. HEALTH EFFECTS

processes responsible for producing 2-butoxyacetic acid. For instance, treatment of rats with pyrazole, an alcohol dehydrogenase inhibitor, provided protection against the hematotoxic effect of 2-butoxyethanol (Ghanayem et al. 1987b). Inhibition of the metabolism of 2-butoxyethanol to butoxyacetaldehyde increased conjugation of the parent compound and urinary excretion of the sulfate or glucuronide detoxification products. Similar results were observed with cyanamide, an aldehyde dehydrogenase inhibitor. Based on observations that 2-butoxyethanol-induced hemolytic anemia was age-dependent, with older rats being more susceptible than younger rats, Ghanayem et al. (1987a) speculated that increased susceptibility of older rats may have been related, in part, to compromised elimination of 2-butoxyacetic acid. Inhibition of renal clearance by the pretreatment of rats with probenecid, an inhibitor of organic acid transport in the proximal renal tubules, significantly increased the half-life of 2-butoxyacetic acid, indicating the importance of renal transport in 2-butoxyacetic acid detoxification (Ghanayem et al. 1990a). Thus, increasing renal transport in exposed individuals might reduce the residence time of the toxic metabolite in the body, consequently reducing the opportunity for toxic reactions.

Ethanol has been shown to block the metabolism of 2-butoxyethanol to 2-butoxyacetic acid through competitive inhibition of alcohol dehydrogenase (Romer et al. 1985). Administration of ethanol after 2-butoxyethanol exposure can be used to control the production of toxic metabolites and to promote conjugation of the parent compound to nontoxic products of elimination such as the glucuronide and sulfate conjugates. This approach has been recommended for clinical therapy for 2-butoxyethanol poisoning (Buckley et al. 1993).

2.10 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 2-butoxyethanol and 2-butoxyethanol acetate is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2-butoxyethanol and 2-butoxyethanol acetate.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce

2. HEALTH EFFECTS

the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.10.1 Existing Information on Health Effects of 2-Butoxyethanol

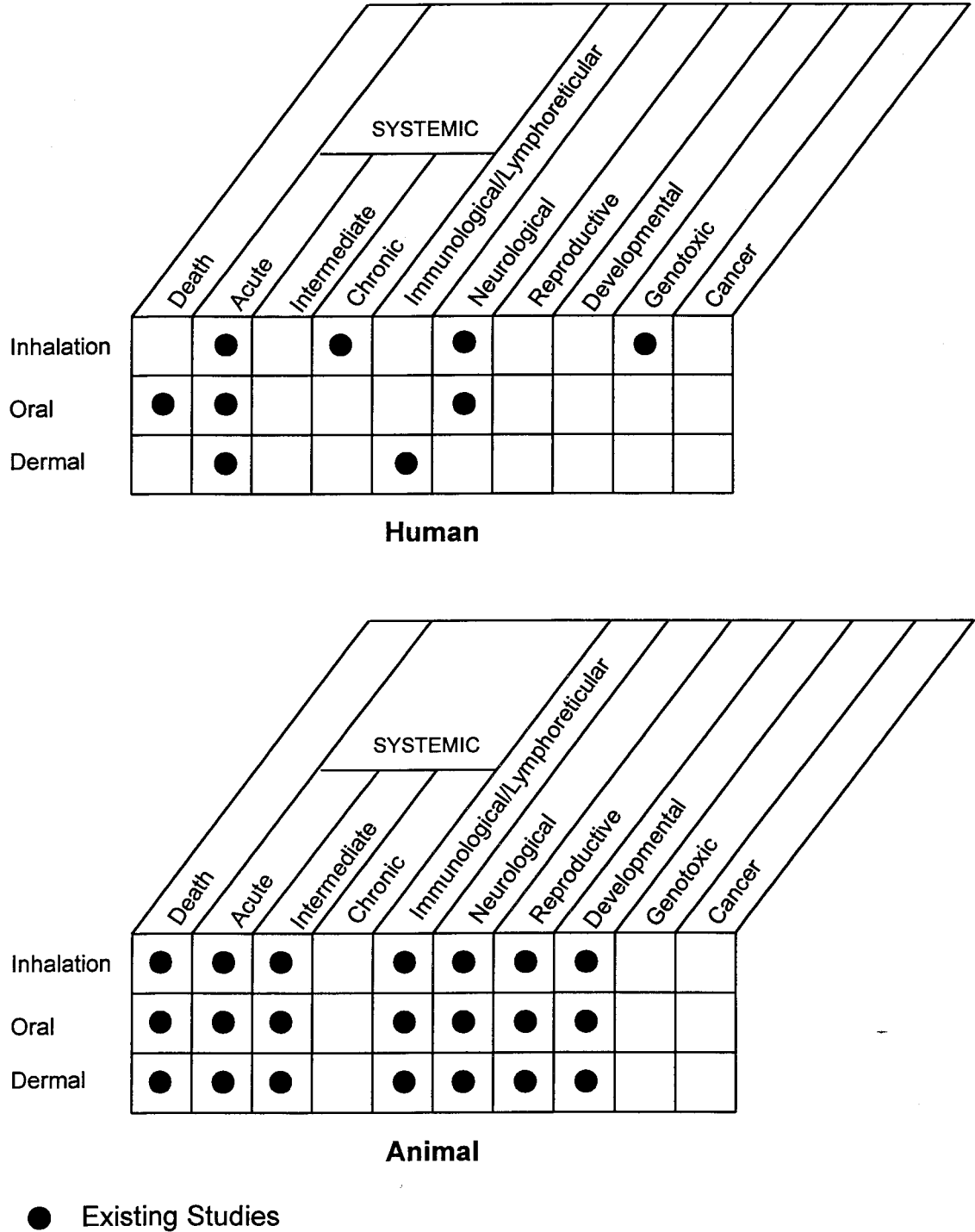
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 2-butoxyethanol and 2-butoxyethanol acetate are summarized in Figures 2- 12 and 2- 13, respectively. The purpose of these figures is to illustrate the existing information concerning the health effects of 2-butoxyethanol and 2-butoxyethanol acetate. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need.” A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Virtually all of the information regarding health effects in humans comes from experimental studies of volunteers exposed by inhalation or dermally to 2-butoxyethanol, or case reports of accidental or intentional poisoning in humans who ingested household products containing 2-butoxyethanol. Exposures to 2-butoxyethanol and 2-butoxyethanol acetate occur in minting and silk screening shops, at furniture manufacturers, in auto body shops, or anywhere that large-scale painting, inking, furniture stripping, or metal stripping or cleaning occurs. In addition, since 2-butoxyethanol and 2-butoxyethanol acetate are contained in many all-purpose cleaning agents, exposure occurs through window, car and floor washing. Consumer products containing 2-butoxyethanol consist primarily of all-purpose cleaners, but some paints, inks, furniture staining and stripping products, and cosmetics also contain these chemicals. Inhalation and dermal absorption are the main routes of exposure, although accidental or intentional poisoning also occurs.

As seen in Figure 2-1 2 for 2-butoxyethanol, inhalation and oral information for humans is available describing acute-duration systemic and neurological effects. A case report describing the death of a woman following ingestion of a cleaner containing 2-butoxyethanol is also available. A study report of genotoxic effects in humans following occupational exposure to 2-butoxyethanol and the structurally similar 2-ethoxyethanol is

2. HEALTH EFFECTS

FIGURE 2-12. Existing Information on Health Effects of 2-Butoxyethanol



2. HEALTH EFFECTS

FIGURE 2-13. Existing Information on Health Effects of 2-Butoxyethanol Acetate

	SYSTEMIC										
	Death	Acute	Intermediate	Chronic	Immunological/Lymphoreticular	Neurological	Reproductive	Developmental	Genotoxic	Cancer	
Inhalation											
Oral											
Dermal		●									

Human

	SYSTEMIC										
	Death	Acute	Intermediate	Chronic	Immunological/Lymphoreticular	Neurological	Reproductive	Developmental	Genotoxic	Cancer	
Inhalation	●	●	●		●	●	●				
Oral	●	●			●	●	●				
Dermal	●	●			●	●	●				

Animal

● Existing Studies

2. HEALTH EFFECTS

available. Information describing the effects of human dermal exposure is limited, consisting of acuteduration systemic and immunological effects. Inhalation, oral, and dermal studies in animals have provided information on death, acute- and intermediate-duration systemic effects, and immunological and lymphoreticular, neurological, reproductive, and developmental effects.

For 2-butoxyethanol acetate, data describing health effects in humans are limited to a dermal irritancy study (Figure 2- 13). Animal studies with 2-butoxyethanol acetate are extremely limited but provide some information on death; acute-duration systemic effects; and immunological and lymphoreticular, neurological, reproductive, and developmental effects after inhalation and oral exposure. In addition, information exists on intermediate-duration systemic effects after inhalation exposure. Dermal studies in animals provide information on death; acute-duration systemic effects; and immunological and lymphoreticular, neurologic, and reproductive effects. It should be noted that the information for 2-butoxyethanol acetate is contained in only two studies.

2.10.2 Identification of Data Needs

Acute-Duration Exposure. There are reports on the health effects resulting from acute exposure in a limited number of studies of humans, and more from animals exposed to 2-butoxyethanol via the inhalation, oral, and dermal routes. In humans exposed by inhalation to 2-butoxyethanol, nasal, throat, and eye irritation, and possibly emesis have been identified as effects (Carpenter et al. 1956). In humans who ingested 2-butoxyethanol, respiratory, cardiovascular, hematological, hepatic, renal, ocular, and metabolic effects have been identified (Bauer et al. 1992; Gijzenbergh et al. 1989; Gualtieri et al. 1995; Litovitz et al. 1991; Rambourg-Schepens et al. 1988). Death also occurred in one of these cases (Litovitz et al. 1991). Very little information exists for health effects resulting from dermal exposure of humans, and the data indicate minor local dermal effects and no dermal sensitivity (CMA 1992; Greenspan et al. 1990; Johanson et al. 1988). The primary target organs for acute exposure are the hematological, hepatic, renal, and lymphoreticular (spleen) systems.

In acute-duration inhalation studies in animals, systemic effects have been observed as follow; respiratory effects (Carpenter et al. 1956; Dodd et al. 1983; Dow 1986; Kane et al. 1980; Tyl et al. 1984), gastrointestinal effects (Carpenter et al. 1956; Dow 1986), hematological effects (Carpenter et al. 1956; Dodd et al. 1983; Sabourin et al. 1992a; Tyl et al. 1984; Werner et al 1943a), hepatic effects (Carpenter et al. 1956; Dodd et al. 1983; Dow 1986), renal effects (Carpenter et al. 1956; Dodd et al. 1983; Doe 1984; Dow 1986; Nelson et al. 1984; Tyl et al. 1984; Werner et al. 1943a), ocular effects (Dow 1986; Tyl et al. 1984), and body weight

2. HEALTH EFFECTS

effects (Carpenter et al. 1956; Dodd et al. 1983; Dow 1972; Tyl et al. 1984). The acute inhalation data were sufficient to derive an acute inhalation MRL of 6 ppm based on a NOAEL of 50 ppm for hematological effects in rats in the study by Tyl et al. (1984).

In acute-duration oral studies in animals, systemic effects have been observed as follows: respiratory effects (Carpenter et al. 1956; Dow 1981; NTP 1989; Union Carbide 1980b; Wier et al. 1987), gastrointestinal effects (Olin 1976; Shepard 1994b; Union Carbide 1980b), hematological effects (Carpenter et al. 1956; Corley et al. 1994; Ghanayem and Sullivan 1993; Ghanayem et al. 1987a, 1987b, 1990b, 1992; Grant et al. 1985; NTP 1989; Sivarao and Mehendale 1995), muscular effects secondary to neurotoxicity (Olin 1976), hepatic effects (Carpenter et al. 1956; Ghanayem et al. 1987b, 1992; Grant et al. 1985; NTP 1989; Olin 1976; Union Carbide 1980b), renal effects (Carpenter et al. 1956; Dow 1959; Ghanayem et al. 1987a, 1987b; Grant et al. 1985; NTP 1989; Olin 1976; Sivarao and Mehendale 1995; Union Carbide 1980b), possible dermal effects (Dow 1981; NTP 1989; Olin 1976), ocular effects (Dow 1981; NTP 1989), and body weight effects (Grant et al. 1985; Hat-din et al. 1987; Heindel et al. 1990; NTP 1989, 1993; Union Carbide 1980b; Schuler et al. 1984; Wier et al. 1987). The acute oral data were sufficient to derive an acute oral MRL of 0.4 mg/kg/day based on a LOAEL of 32 mg/kg for hematological effects in rats in the study by Ghanayem et al. (1987b).

In acute-duration dermal studies in animals, systemic effects have been observed as follows: respiratory effects (Duprat and Gradiski 1979; Union Carbide 1980b), gastrointestinal effects (Union Carbide 1980b), hematological effects (Bartnik et al. 1987; Carpenter et al. 1956; Duprat and Gradiski 1979; Hardin et al. 1984; Union Carbide 1980a), muscular effects secondary to neurotoxicity (Olin 1976), hepatic and renal effects (Carpenter et al. 1956; Duprat and Gradiski 1979; Olin 1976; Union Carbide 1980a, 1980b), dermal effects (Dow 1959; Duprat and Gradiski 1979; Hardin et al. 1984; Rohm and Haas 1983; Union Carbide 1980a, 1980b; Zissu 1995), ocular effects (Dow 1959; Kennah et al. 1989a; Olin 1976; Rohm and Haas 1983; Union Carbide 1980a, 1980b), and body weight effects (Dow 1959; Hardin et al. 1984; Union Carbide 1980a).

Information is also available for levels that cause death in a number of animals species following inhalation exposure (Carpenter et al. 1956; Dodd et al. 1983; Dow 1986; Nelson et al. 1984; Sabourin et al. 1992a; Tyl et al. 1984; Werner et al. 1943a), oral exposure (Carpenter et al. 1956; Dow 1959, 1981; Eastman Kodak 1983, 1988; Hardin et al. 1987; Heindel et al. 1990; Kennedy and Graepel 1991; Krasavage 1986; NTP 1989; Olin 1976; Sivarao and Mehendale 1995; Smialowicz et al. 1992; Union Carbide 1980b; Schuler et al. 1984;

2. HEALTH EFFECTS

Shepard 1994b; Smyth et al. 1941), and dermal exposure (Carpenter and Condra 1961; Carpenter et al. 1956; Dow 1959; Duprat and Gradiski 1979; Eastman Kodak 1988; Olin 1976; Union Carbide 1980a, 1980b) to 2-butoxyethanol. Studies have shown that rats are particularly sensitive to the hematotoxic effects of 2-butoxyethanol, compared to humans (Bartnik et al. 1987; Ghanayem and Sullivan 1993; Udden 1994). However, since numerous data are available regarding systemic effects in animals, more studies on species-specific systemic effects, particularly hematotoxicity, after acute-duration exposure by inhalation, oral, and dermal routes in animals would not be particularly useful. Doses or concentrations that would result in hematological effects in humans are not known, and it would be unethical to find out by direct experiments on humans; however, there may be a place for more *in vitro* experiments on fresh human blood.

The only information regarding health effects in humans resulting from acute exposure to 2-butoxyethanol acetate is a study by Jacobs et al. (1989), who found mild erythema in humans after acute dermal exposure. Very few data are available describing health effects in animals following inhalation, oral, or dermal exposure for acute-duration exposure. The data found are principally contained in three articles (Jacobs et al. 1989; Truhaut et al. 1979; Zissu 1995). Although hematology was performed in the acute-duration inhalation study conducted in rats and rabbits by Truhaut et al. (1979), only one exposure concentration was used, and selected organs were examined only for gross pathology. No effects were observed in rats, and hemoglobinuria and/or hematuria were the only effects noted for rabbits. For an acute-duration oral study on 2-butoxyethanol acetate in rats conducted by Truhaut et al. (1979), LD₅₀ data were provided, gross and histological examinations were performed, and hemoglobinuria and renal effects were observed, but the doses used were not specified. In the acute dermal study in rabbits conducted by Truhaut et al. (1979), an LD₅₀ value was determined, gross and histological examinations were performed, and hematological and renal effects were observed at $\geq 3,191$ mg/kg. In the study by Jacobs et al. (1989), the only information provided was that dermal exposure of rabbits to 2-butoxyethanol acetate resulted in slight erythema. 2-Butoxyethanol acetate was considered a moderate irritant by the Draize protocol and non-irritating by the European Economic Communities protocol (Zissu 1995).

Although 2-butoxyethanol acetate is readily metabolized to 2-butoxyethanol and both compounds are metabolized by the same pathways, the limited data indicate that dose-response data for the acetate may be different from that for 2-butoxyethanol. For example, the oral LD₅₀ values for male Wistar rats were reported to be 1,590 mg/kg for 2-butoxyethanol (Olin 1976) and 3,000 mg/kg for 2-butoxyethanol acetate in olive oil (Truhaut et al. 1979). The contribution of a vehicle effect on the difference in toxicity between 2-butoxyethanol and the acetate is not known; it is also unknown whether there are differences in absorption between

2. HEALTH EFFECTS

the two compounds. Other toxicological data for 2-butoxyethanol acetate are too limited to permit comparison with the toxicological data for 2-butoxyethanol for the same species, strains, and exposure conditions.

Additional animal or human data on the toxic effects of 2-butoxyethanol acetate by all routes would be useful in assessing the human risk of exposure to 2-butoxyethanol acetate. Characterization of the relative toxicity of 2-butoxyethanol acetate compared to 2-butoxyethanol would aid in the use of data already generated for 2-butoxyethanol in predicting risk factors of exposure to the acetate form. In addition, clarification of species-specific toxicity, similar to that observed for 2-butoxyethanol, would aid in understanding the risk associated with exposure to 2-butoxyethanol acetate.

Intermediate-Duration Exposure. No studies were located regarding health effects in humans following intermediate-duration exposure to 2-butoxyethanol by inhalation, oral, or dermal routes. Studies were located regarding systemic effects in animals following intermediate-duration exposure to 2-butoxyethanol by inhalation, oral, and dermal routes. In intermediate-duration inhalation studies in animals, systemic effects have been observed as follows: respiratory effects (Carpenter et al. 1986; Werner et al. 1943b), gastrointestinal effects, renal effects, body weight effects (Carpenter et al. 1956), and hematological effects (Carpenter et al. 1956; Dodd et al. 1983; Werner et al. 1943b). The intermediate inhalation data were sufficient to derive an intermediate inhalation MRL of 3 ppm based on a NO&L of 25 ppm for hematological effects in rats in the study by Dodd et al. (1983). In intermediate-duration oral studies in animals, systemic effects have been observed as follows: gastrointestinal effects (NTP 1993), hematological effects (Eastman Kodak 1983; Krasavage 1986; Nagano et al. 1979,1984; NTP 1993), hepatic effects and renal effects (Carpenter et al. 1956; Eastman Kodak 1983; Heindel et al. 1990; Krasavage 1986; NTP 1993; Weil and Carpenter 1963), and body weight effects (Carpenter et al. 1956; NTP 1993; Weil and Carpenter 1963). The intermediate oral data were sufficient to derive an intermediate oral MRL of 0.07 mg/kg/day for hepatic effects in rats based on the study by NTP (1993). Only one intermediate-duration dermal study was located. In this study (CMA 1983), rabbits were treated dermally for 90 days at ≤ 150 mg/kg, and comprehensive hematology and histological examinations were performed for all relevant systemic organs. The only treatment-related effects were slight to moderate erythema and edema at ≥ 10 mg/kg/day.

The hematological system is the primary target for 2-butoxyethanol toxicity. Therefore, further animal studies designed to confirm and extend the data of Dodd et al. (1983) for inhalation exposure, and animal studies for intermediate-duration exposure by oral administration would be helpful in defining the NOAEL for hematological, hepatic, and renal effects, since these effects occurred at the lowest doses tested (the intermediate oral MRL is based on a LOAEL). Additionally, although some data exist that describe health

2. HEALTH EFFECTS

effects of 2-butoxyethanol in rabbits after intermediate dermal exposure (CMA 1983), studies using higher doses might define target organs and doses that cause hematological effects. These data are important, since dermal exposure to 2-butoxyethanol vapor and aqueous solutions is a primary route of human exposure. Furthermore, there are populations surrounding hazardous waste sites that might be exposed to 2-butoxy-ethanol for intermediate durations.

No studies were located regarding health effects in humans after inhalation, oral, or dermal intermediate-duration exposure to 2-butoxyethanol acetate. No studies were located regarding health effects in animals after intermediate-duration oral or dermal exposure to 2-butoxyethanol acetate. Limited data are available describing health effects in animals following intermediate-duration inhalation exposure. The data found are contained in one article (Truhaut et al. 1979). In this study, in which rats and rabbits were exposed to only one concentration of 2-butoxyethanol acetate (400 ppm for 11 months or 100 ppm for 10 months), histological examinations of several organs identified serious hematological (hemoglobinuria) and renal effects in rats and rabbits. Additional studies defining dose-response data for these and other possible effects of 2-butoxyethanol acetate after intermediate-duration exposure and clarifying how it relates to 2-butoxyethanol would be useful in predicting human toxicity to 2-butoxyethanol acetate exposure.

Chronic-Duration Exposure and Cancer. Statistically significant changes in hematocrit (decrease) and mean corpuscular hemoglobin concentration (increase) were reported in men occupationally exposed to 0.46-0.75 ppm 2-butoxyethanol for 1-6 years (Haufrond et al. 1997). The changes were small, showed no relationship to exposure concentration and were still within normal biological variability. Although the effects may be early indicators of potential adverse effects in humans, and they are consistent with effects in animals, ATSDR considers the average exposure (0.6 ppm) to be a NOAEL. This study serves as the basis of the chronic-duration inhalation MRL of 0.2 ppm. No effects on serum creatinine, urinary retinol binding protein, or serum transaminase levels were noted.

No studies were located regarding health effects in humans or animals after chronic inhalation, oral, or dermal exposure or in animals after chronic inhalation exposure to 2-butoxyethanol or 2-butoxyethanol acetate. The primary targets for adverse systemic effects of 2-butoxyethanol following acute- and intermediate-duration exposure are the hematological and renal systems. Since chronic low-level exposure to 2-butoxyethanol and the acetate form by the inhalation, oral, or dermal routes is possible for populations living near waste sites containing these chemicals, inhalation, oral, and dermal studies on health effects of chronic exposure to

2. HEALTH EFFECTS

2-butoxyethanol and 2-butoxyethanol acetate in animals would be useful in defining potential adverse health effects.

No studies were located regarding carcinogenic effects in humans or animals after exposure to 2-butoxyethanol and 2-butoxyethanol acetate by any route. These compounds have not been classified for carcinogenic effects by the Department of Health and Human Services (DHHS), the National Toxicology Program (NTP), the International Agency for Research on Cancer (IARC), or the Environmental Protection Agency (EPA). Histological examination of comprehensive organs and tissues in animals in chronic studies performed by any route of exposure would be useful in determining potential carcinogenic effects of 2-butoxyethanol or 2-butoxyethanol acetate; however, the genotoxicity data available for 2-butoxyethanol suggest that it is unlikely to cause cancer by damaging DNA.

Genotoxicity. The only *in vivo* study was in workers exposed to both 2-butoxyethanol and the structurally related 2-ethoxyethanol (Sohnlein et al. 1993). No increases in micronuclei or sister chromatid exchanges were observed in these workers. Several reports of *in vitro* studies were found (Chiewchanwit and Au 1995; Gollapudi et al. 1996; Hoflack et al. 1995; Kvelland 1988; McGregor 1984; Tyler 1982). [¹⁴C]2-Butoxy-ethanol was positive in a test that monitored increases in DNA-associated radioactivity in rat primary hepatocytes (McGregor 1984). However, 2-butoxyethanol was negative in tests of mutagenicity with bacteria (Kvelland 1988) and sister chromatid exchange (Tyler 1982) or mutations (Chiewchanwit and Au 1995) in Chinese hamster ovary cells, with or without metabolic activation. 2-Butoxyethanol was negative for mutation in *Salmonella typhimurium* strains TA98, TA100, and TA102 both with and without rat S-9 activation (Hoflack et al. 1995). In *S. typhimurium* strain TA97a 2-butoxyethanol tested positive for mutation both with and without S-9 activation. The mutation assay of 2-butoxyethanol in strain TA97a was repeated by Gollapudi et al. (1996). In this study, 2-butoxyethanol was negative for mutations both with and without rat S-9 metabolic activation, and it was negative in *E. coli* WP2uvrA strain. Gollapudi et al. (1996) suggested that Hoflack et al. (1995) found positive results because they used 2-butoxyethanol contaminated with higher levels of peroxides, which test positive in strain TA97a. The 2-butoxyethanol used by Gollapudi et al. (1996) contained 23 ppm of peroxides which was measured just before the tests. The 2-butoxyethanol used by Hoflack et al. (1995) contained less than 50 ppm peroxides; the information was provided by the manufacturer, so the actual concentrations of peroxides may have been higher. Gollapudi et al. (1996) concluded that peroxides and/or experimental variables probably account for the difference in results observed in their study and the study by Hoflack et al. (1995). The available data suggest that 2-butoxyethanol is not genotoxic. The exception may be when it is contaminated with peroxides. No studies were located regarding

2. HEALTH EFFECTS

genotoxicity of 2-butoxyethanol acetate. Further studies of 2-butoxyethanol and 2-butoxyethanol acetate in *vivo* and *in vitro* would more fully determine the genotoxic potential of these compounds.

Reproductive Toxicity. No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal exposure to 2-butoxyethanol or 2-butoxyethanol acetate.

For 2-butoxyethanol, two inhalation (800 ppm for 3 hours; \leq 867 ppm for 4 hours; \leq 245 ppm for 9 days; \leq 77 ppm for 13 weeks) studies (Dodd et al. 1983; Doe 1984), several oral (\leq 500 mg/kg administered once; 500 or 1,000 mg/kg for 4 days; \leq 346 or \leq 627 mg/kg/day for 2 weeks) studies (Eastman Kodak 1983; Exon et al. 1991; Ghanayem et al. 1987; Grant et al. 1985; Heindel et al. 1990; Krasavage 1986; Nagano et al. 1979, 1984; NTP 1993), and two dermal (doses up to 150 mg/kg/day for 90 days or 18-361 mg/kg/day for 11 days) studies (CM4 1983; Union Carbide 1980a) in animals measured testicular weight and/or performed histological examination of male reproductive organs and found no effect. However, one intermediateduration oral (\leq 443 mg/kg/day for 60 days) study found decreased sperm concentration in male rats (NTP 1993), and a go-day study reported testicular atrophy in rats (Weil and Carpenter 1963). In the go-day dermal study (doses of up to 150 mg/kg/day) in rabbits (CMA 1983), there was only a slight increase in testicular weight of rabbits. Reproductive effects (implantation loss, decreases in live fetuses, and/or increase in nonviable implants) have been found in pregnant rats and rabbits exposed to 2-butoxyethanol(200 ppm) by inhalation during gestation (Tyl et al. 1984). In oral (\leq 363 mg/kg/day for 13 weeks) studies, female rats, but not female mice, had altered estrous cycles (NTP 1993, although the total duration of the cycle was not altered. Pregnant rats (treated with 600 mg/kg/day on gestation days 9-11 or 11-13) had vaginal bleeding, increased resorptions, and implantation loss (NTP 1989), and pregnant mice (treated with 1,180 mg/kg/day on gestation days 6-13) had decreases in viable litters (Hardin et al. 1987; Schuler et al. 1984) and increased resorptions (Wier et al. 1987). In a breeding-pair study in male and female mice (treated with 1,300 or 2,100 mg/kg/day for 21 weeks), there was a decrease in the number of litters produced per pair that was found to be a result of effects on female reproduction in cross-mating experiments (Heindel et al. 1990). However, in the NTP (1993) drinking water study, histological examination of female rat and mouse reproductive organs (NTP 1993), and vaginal cytology evaluations of rats and/or mice revealed no pathology. Histological examination of the reproductive organs of female rabbits in the go-day dermal study by CMA (1983) also revealed no pathology. Since several studies that performed histological examination of reproductive organs of animals exposed by all routes were negative, additional studies of this kind do not appear to be useful. One oral continuous breeding study was performed in mice, a drinking water study (Heindel et al. 1990) that has also been summarized in Morrissey et al. (1988, 1989). An oral reproductive study in rats and reproductive

2. HEALTH EFFECTS

studies in two species conducted by the inhalation and dermal routes (which are the two routes most relevant for humans) would help to complete the picture of reproductive effects of 2-butoxyethanol in animals and help to determine whether 2-butoxyethanol exposure presents a reproductive hazard to humans.

For 2-butoxyethanol acetate, no gross pathological lesions were found in the testes or ovaries of rats or rabbits exposed to 400 ppm for 4 hours and no gross or histopathological lesions were found in the testes or ovaries of rats or rabbits exposed by inhalation intermittently to 400 ppm for 1 month or 100 ppm for 10 months, in rats at unspecified single gavage doses, or in rabbits exposed dermally at $\leq 10,000$ mg/kg for 24 hours (Truhaut et al. 1979). However, no reproductive function studies were located.

The results of both 2-butoxyethanol and 2-butoxyethanol acetate studies indicate that further histological examination of male and female reproductive organs would not be particularly useful, but reproductive studies in mated pairs of two species exposed to 2-butoxyethanol acetate by all routes would be useful to determine the reproductive toxicity potential of this compound.

Developmental Toxicity. No studies were located regarding developmental effects in humans after inhalation, oral, or dermal exposure to 2-butoxyethanol or 2-butoxyethanol acetate.

Developmental effects have been observed in animals after inhalation, oral, and dermal exposure to 2-butoxyethanol. In inhalation studies on 2-butoxyethanol in animals, the developmental effects consisted of retarded skeletal ossification in the offspring of pregnant rats and pregnant rabbits (Tyl et al. 1984). In oral studies, the developmental effects consisted of decreased fetal body weight of the rats and decreased gravid uterine weight of the rat dams (NTP 1989), some evidence of cleft palate in the fetuses of pregnant mice (Wier et al. 1987), and decreased pup weight in the offspring of mating pairs of rats (Heindel et al. 1990). In dermal studies, no developmental effects were observed in the offspring of pregnant rats exposed at 0.48 mL/day during gestation (Hardin et al. 1984). A higher dermal dose (1.4 mL/day) caused mortality of the dams. With the exception of decreased pup weight observed in mice (Heindel et al. 1984), developmental effects reported occurred at 2-butoxyethanol doses that resulted in moderate to severe maternal toxicity (Hardin et al. 1987; NTP 1989; Tyl et al. 1984; Wier et al. 1987). An additional developmental study on 2-butoxyethanol by the dermal route in another species (mouse or rabbit) would be useful, since dermal exposure to 2-butoxyethanol in cleaning solutions is a primary route of exposure in the general population.

2. HEALTH EFFECTS

No studies were located regarding developmental effects in animals after inhalation, oral, or dermal exposure to 2-butoxyethanol acetate. Studies of the developmental toxicity of this compound by inhalation, oral, and dermal routes would be useful in predicting potential developmental toxicity, and relating the toxicity of 2-butoxyethanol acetate to 2-butoxyethanol.

Immunotoxicity. No studies were located regarding immunological and lymphoreticular effects in humans after inhalation or oral exposure to 2-butoxyethanol or 2-butoxyethanol acetate. Slight erythema, but no allergic reaction, was noted on skin-patch tests with 2-butoxyethanol acetate in humans (Jacobs et al. 1989). A limited human dermal sensitivity study in 201 persons with 10% 2-butoxyethanol showed no overt effect (CMA 1992). The 10% concentration was tested because it is the highest concentration found in cosmetics. 2-Butoxyethanol has also tested negative for dermal sensitization in guinea pigs using the maximized Magnusson and Kliman test (Zissu 1995).

In two oral studies, the information on immunological effects of 2-butoxyethanol in animals consists of the findings that no effect on the immune system was found in rats (Exon et al. 1991; Smialowicz et al. 1992), and no effect on thymus and spleen weight and no histopathological lesions in the thymus were observed in rats (Exon et al. 1991).

Studies in animals describe effects on the spleen, many of which are related to the hematological effect of 2-butoxyethanol. In inhalation studies, splenic effects consisted of increased spleen weight of pregnant rats (Tyl et al. 1984). In oral studies, splenic and other lymphoreticular effects in animals consisted of increased spleen weight (Eastman Kodak 1983; Ghanayem et al. 1987a, 1987b, 1992; Grant et al. 1985; Krasavage 1986; NTP 1989), extramedullary splenic hematopoiesis (Grant et al. 1985), splenic congestion and enlarged dark spleens (Eastman Kodak 1983; Krasavage 1986), hemosiderosis in the spleen, decreased thymus weight, and bone marrow hyperplasia and increased hematopoiesis (NTP 1993). In dermal studies on 2-butoxyethanol in animals, effects on lymphoreticular organs consisted of congestion in the spleen, erythrocytic infiltration, and white atrophic pulp (Duprat and Gradiski 1979); engorged spleen (Carpenter et al. 1956); and enlarged and dark red spleen (Union Carbide 1980a, 1980b).

One reasonably thorough study examined immune function in rats orally dosed at up to 400 mg/kg/day 2-butoxyethanol twice after immunization with trinitrophenyl-lipopolysaccharide (TNP-LPS) (Smialowicz et al. 1992). Compared with controls, the 2-butoxyethanol had no adverse effect on antibody production, delayed B type hypersensitivity, natural killer cell function, or splenocyte production of cytokines.

2. HEALTH EFFECTS

Since the effects on the spleen and bone marrow are secondary to the hemolytic effects of 2-butoxyethanol, and since a number of studies performed histological examination of lymphoreticular organs, additional studies on lymphoreticular effects do not appear to be useful. However, the potential for immunotoxicity of 2-butoxyethanol has not been sufficiently studied. A battery of immunotoxicity tests conducted by all routes, but particularly by the inhalation and dermal routes (the most relevant routes for humans) would help to determine whether 2-butoxyethanol is immunotoxic.

For 2-butoxyethanol acetate, no gross or histopathological lesions were found in the spleen of rats or rabbits exposed by inhalation intermittently to 400 ppm for 1 month or to 100 ppm for 10 months, in rats at unspecified single gavage doses, or in rabbits exposed dermally at $\leq 10,000$ mg/kg for 24 hours (Truhaut et al. 1979). Studies such as those suggested for 2-butoxyethanol would be helpful not only in defining the effect of 2-butoxyethanol acetate on the immune system, but also in relating it to the toxicity of 2-butoxyethanol.

Neurotoxicity. The only information on neurological effects in humans exposed to 2-butoxyethanol is that humans exposed experimentally by inhalation experienced headache and disturbed taste sensation (Carpenter et al. 1956), and that people who intentionally ingested household cleaning agents containing 2-butoxyethanol became comatose (Bauer et al. 1992; Gijzenbergh et al. 1989; Eitovitz et al. 1991; Rambourg-Schepens et al. 1988).

Neurological effects have been observed in animals after inhalation, oral, and dermal exposure to 2-butoxyethanol. In inhalation studies of 2-butoxyethanol in animals, neurological effects consisted of loss of coordination (Dodd et al. 1983), extreme weakness and apathy (Carpenter et al. 1956), excessive salivation (Dow 1972, 1986), and poor coordination of the extremities and loss of equilibrium (Dow 1986). In oral studies of 2-butoxyethanol in animals, neurological effects consisted of sluggishness, prostration, narcosis, lethargy, failure to right, and/or ataxia (Carpenter et al. 1956; Dow 1959, 1981; Eastman Kodak 1983; Krasavage 1986; NTP 1989; Olin 1976; Sivarao and Mehendale 1995; Shepard 1994b; Union Carbide 1980b; Wier et al. 1987). In dermal studies of 2-butoxyethanol in animals, neurological effects consisted of prostration, narcosis, convulsion, nystagmus, anorexia, lack of spontaneous movement, and/or inactivity (Duprat and Gradiski 1979; Hardin et al. 1984; Olin 1976; Union Carbide 1980a). Most of these effects occurred in animals prior to death at high lethal doses. In intermediate-duration inhalation (Dodd et al. 1983) oral (Eastman Kodak 1983; Krasavage 1986; NTP 1993), and dermal (CMA 1983) studies, comprehensive histological examinations of the brain, spinal cord, and/or sciatic nerves revealed no lesions.

2. HEALTH EFFECTS

For 2-butoxyethanol acetate, no clinical signs of neurotoxicity and no histopathological lesions in the brain were found in rats or rabbits exposed by inhalation intermittently to 400 ppm for 1 month or to 100 ppm for 10 months, in rats at unspecified single gavage doses, or in rabbits exposed dermally at $\leq 10,000$ mg/kg for 24 hours (Truhaut et al. 1979).

A battery of neurological and behavioral tests in animals after inhalation, oral, and dermal exposure would help to determine whether 2-butoxyethanol and 2-butoxyethanol have more subtle neurobehavioral effects.

Epidemiological and Human Dosimetry Studies. Studies of human populations exposed to 2-butoxyethanol or 2-butoxyethanol acetate primarily involve evaluations of kinetic parameters and biomonitoring for occupational exposure after inhalation or dermal exposure (Angerer et al. 1990; Haufroid et al. 1997; Johanson and Boman 1991; Johanson and Johnsson 1991; Johanson et al. 1986a, 1988; Rettenmeier et al. 1993; Sakai et al. 1994; Vincent et al. 1993). Hematological effects have been examined in a small group of men occupationally exposed to 2-butoxyethanol and methyl ethyl ketone (Haufroid et al. 1997). Small but statistically significant changes in hematocrit (decrease) and mean corpuscular hemoglobin concentration (increase) that were still within normal biological variability were reported. Although the effects may be early indicators of potential adverse effects in humans, and they are consistent with effects in animals, ATSDR considers the average exposure (0.6 ppm) to be a NOAEL. This study serves as the basis of the chronic-duration inhalation MRL of 0.2 ppm. The study authors indicated that the hematological effects should be confirmed in additional populations exposed to 2-butoxyethanol. One study regarding genotoxicity and exposure assessment in workers exposed to both 2-butoxyethanol and 2-ethoxyethanol (Sohnlein et al. 1993) is available. Occupational exposure to 2-butoxyethanol and 2-butoxyethanol acetate by the inhalation or dermal route comprises a large proportion of the potential exposure in the population. Thus, epidemiological studies of humans exposed occupationally, or at or near hazardous waste sites would provide valuable information on the potential toxicity of the compound. This information would be useful, especially in light of the apparent species differences in relative toxicity.

Biomarkers of Exposure and Effect

Exposure. The presence of 2-butoxyacetic acid in the urine is the accepted biomarker of exposure for both 2-butoxyethanol and 2-butoxyethanol acetate (Johanson et al. 1989), and it has been used as a biomarker in surveys of occupational exposure; 2-butoxyethanol in the blood and urine or 2-butoxyacetic acid and its glutamine conjugate in urine have also been used as biomarkers (Angerer et al. 1990; Haufroid et al. 1997;

2. HEALTH EFFECTS

Johanson and Boman 1991; Johanson and Fernstrom 1986; Johanson and Johnsson 1991; Johanson et al. 1986a, 1988, 1989; Johnsson and Steen 1978; Rettenmeier et al. 1993; Sakai et al. 1994; Vincent et al. 1993). These have also been used as biomarkers of exposure in animal experiments (Ghanayem et al. 1987a, 1987b, 1987c, 1992; Medinsky et al. 1990; Romer et al. 1985; Sabourin et al. 1992a, 1992b, 1993). More recently, analytical methods have been able to detect 2-butoxyacetic acid in human blood (Johanson and Johnsson 1991). These biomarkers are unique, relatively short-lived, and serve well for monitoring exposure. However, the exact relationship between blood or urine levels of these compounds and exposure by the inhalation, oral, or dermal routes is still not clear; some of this may be due to measurement of only free 2-butoxyacetic acid in the urine rather than the total of free and conjugates. Additional studies of exposure and blood and urine levels of these compounds would be helpful in predicting the health effects of exposure in the occupational setting, and in instances of exposure of populations near waste sites, or those using consumer products containing 2-butoxyethanol or the acetate form. An exploratory study of the role of genetic polymorphism of CYP 2E1 on 2-butoxyethanol metabolism by humans would also be useful. Haufroid et al. (1997) looked at urinary metabolites in a small sample of humans exposed to 2-butoxyethanol; the study included 30 c1/c1 homozygotes and one c1/c2 heterozygote. Individuals heterozygous for the c2 allele may produce less 2-butoxyethanol acid, and more ethylene glycol than individual homozygous for the c1 allele; however, ethylene glycol and its metabolites were not measured in the urine in this study and only free butoxyacetic acid, not conjugates, was measured.

Effect. Monitoring of hematological parameters may be useful as a biomarker of effect of 2-butoxyethanol and 2-butoxyethanol acetate. Toxic effects occur in the red blood cells and are either from 2-butoxyethanol or its metabolites (Bartnik et al. 1987; Ghanayem et al. 1987a, 1987b). However, hematological effects are not specific to 2-butoxyethanol. The tests cannot be relied upon to find preclinical disease, but may be useful in identifying changes that are early indicators of effects. Furthermore, these markers of effect may not be useful for long periods following cessation of exposure, nor do they distinguish between acute and chronic exposure. The use of urinary D-glucaric acid as a biomarker of effect following exposure to 2-butoxyethanol has been examined in foundry workers exposed to the compound in paints (Collinot et al. 1996). Although measurement of D-glucaric acid is not an effect specific to 2-butoxyethanol exposure, the study authors concluded that it was more sensitive than a standard blood count. Further investigation of possible biomarkers of 2-butoxyethanol or 2-butoxyethanol acetate exposure would be helpful in monitoring the health effects of these chemicals.

2. HEALTH EFFECTS

Absorption, Distribution, Metabolism, and Excretion. Data from both humans (Angerer et al. 1990; Johanson and Boman 1991; Johanson and Johnsson 1991; Johanson et al. 1986a, 1989) and rats (Johanson 1994; Sabourin et al. 1992a) indicate that 2-butoxyethanol is rapidly and extensively absorbed through the lungs. No studies were located regarding pulmonary absorption in other animal species. Although no experimentally acquired data were available on gastrointestinal absorption of 2-butoxyethanol in humans, some data are available from case reports of oral poisonings, which suggest that absorption from the gastrointestinal system is rapid (Bauer et al. 1992; Gijzenbergh et al. 1989; Gualtieri et al. 1995; Litovitz et al. 1991; Rambourg-Schepens et al. 1988). Data from rat studies corroborate these results (Corley et al. 1994; Ghanayem et al. 1987c; Medinsky et al. 1990), but no data were available for other animal species. Studies in humans exposed experimentally (Corley et al. 1997; Johanson and Boman 1991; Johanson et al. 1988) or occupationally (Vincent et al. 1993) indicate that 2-butoxyethanol can be absorbed through the skin, both from the vapor and from the liquid form. Results suggest that persons that expose large portions of their skin to the liquid form of 2-butoxyethanol are at risk of absorbing acutely toxic doses. *In vitro* studies using human skin also indicate dermal absorption (Bartnik et al. 1987; Dugard et al. 1984). Data from rats (Bartnik et al. 1987; Sabourin et al. 1992b, 1993) and guinea pigs (Johanson and Fernstrom 1986) exposed dermally support this conclusion. An *in vitro* study using skin from humans, rats, and pigs shows that the absorption of neat 2-butoxyethanol was initially slower than from aqueous solutions, such as all purpose cleaners (Bartnik et al. 1987).

No information on distribution of 2-butoxyethanol to tissues in humans was located. Following absorption into the body, 2-butoxyethanol was widely distributed from the blood to tissues of rats after inhalation (Johanson 1994), oral (Ghanayem et al. 1987b, 1987c), and dermal (Bartnik et al. 1987) exposure.

There is no evidence to suggest that the route of administration has any substantial effect on the subsequent metabolism of 2-butoxyethanol in animals, although the route of administration and the dose may alter the relative amounts of individual metabolites (Medinsky et al. 1990; Sabourin et al. 1992a, 1992b, 1993). 2-Butoxyacetic acid (free or glycine or glutamine conjugates) is the major blood and urinary metabolite of 2-butoxyethanol in humans after inhalation exposure (Johanson and Johnsson 1991; Johanson et al. 1986a), while oxalate, formed from metabolism of ethylene glycol (a hydrolysis product of 2-butoxyethanol), was found in the urine of a patient after ingestion (Rambourg-Schepens et al. 1988). 2-Butoxyacetic acid is also the major urinary metabolite in rats, guinea pigs, dogs, rabbits, dogs, and monkeys exposed to 2-butoxyethanol by inhalation (Carpenter et al. 1956). Other metabolites in rats after inhalation, oral, or dermal exposure are expired CO₂, ethylene glycol, and glucuronide and sulfate conjugates of 2-butoxyethanol in the

2. HEALTH EFFECTS

urine, and 2-butoxyacetic acid and 2-butoxyethanol-glucuronide conjugate in the bile (Corley et al. 1994; Ghanayem et al. 1987c; Sabourin et al. 1992a, 1992b, 1993). Based on the rat data, metabolic pathways have been elucidated. 2-Butoxyethanol is oxidized via alcohol dehydrogenase to the aldehyde, then further oxidized to 2-butoxyacetic acid by aldehyde dehydrogenase. 2-Butoxyacetic acid can then be detoxified by conjugation with glycine or glutamine, or it can be broken down to CO₂. 2-Butoxyethanol can also be metabolized to ethylene glycol, another toxic glycol ether, or it can be directly detoxified by conjugation and excreted. Biotransformation of 2-butoxyethanol to 2-butoxyacetic acid is necessary for 2-butoxyethanol-induced toxicity. It is clear, however, that the metabolic pathway can be influenced, thus altering the amount of toxic metabolites and subsequent toxicity. Additional studies on conditions that favor detoxification of the parent compound through conjugation over metabolism of the parent compound to its toxic metabolite 2-butoxyacetic acid would be useful in not only understanding the toxic reactions after exposure, but may also suggest ways to prevent or minimize toxicity after exposure. These studies might include the examination of the effects of polymorphism of CYP 2E1 in humans on the metabolism of 2-butoxyethanol to follow up one study in which a person with one alternate allele had less free 2-butoxyacetic acid in urine than 30 with 2 copies of a common allele (Haufrond et al. 1997).

Respiratory excretion of 2-butoxyethanol consists of expired CO₂ and unchanged parent compound (Bartnik et al. 1987; Ghanayem et al. 1987a; Medinsky et al. 1990; Sabourin et al. 1992a, 1992b, 1993). However, urinary excretion of 2-butoxyethanol, 2-butoxyacetic acid, ethylene glycol, and the conjugates is the primary route in both humans and animals (Bartnik et al. 1987; Carpenter et al. 1956; Ghanayem et al. 1987a, 1987b, 1987c; Gijnsbergh et al. 1989; Johanson 1994; Johanson and Johnsson 1991; Johanson et al. 1986a, 1988; Jijnsson and Steen 1978; Rambourg-Schepens et al. 1988; Rettenmeier et al. 1993; Sabourin et al. 1992a, 1992b, 1993; Sakai et al. 1994; Vincent et al. 1993). 2-Butoxyethanol, 2-butoxyacetic acid, and the glucuronic conjugate of 2-butoxyethanol are also excreted in the bile (Ghanayem et al. 1987a, 1987b, 1987c). Fecal excretion is a minor route (Bartnik et al. 1987; Ghanayem et al. 1987b, 1987c; Medinsky et al. 1990; Sabourin et al. 1992a, 1992b, 1993).

The absorption of 2-butoxyethanol acetate has not been extensively studied, although in humans occupationally exposed to the acetate, 2-butoxyacetic acid was detected in the urine (Johanson et al. 1989), and absorbed doses of the acetate were calculated for rabbits exposed dermally (Truhaut et al. 1979). No studies regarding distribution of 2-butoxyethanol acetate were located. The metabolism of 2-butoxyethanol acetate has not been extensively studied, presumably because 2-butoxyethanol acetate is assumed to be metabolized to 2-butoxyethanol in the body, and then to follow the same pathway as 2-butoxyethanol, since

2. HEALTH EFFECTS

2-butoxyacetic acid has been detected in human urine after 2-butoxyethanol acetate exposure (Johanson et al. 1989). Other than detection of 2-butoxyacetic acid in urine in humans occupationally exposed to 2-butoxy-ethanol acetate, no studies were located regarding excretion of the acetate form.

The absorption, distribution, metabolism, and excretion of 2-butoxyethanol are relatively well understood, leading to a number of PBPK models (Corley 1996; Corley et al. 1994; Johanson 1986, 1991a; Johanson and Naslund 1988; Shyr et al. 1993). These models have been validated with acute- and intermediate-duration pharmacokinetic data. Chronic pharmacokinetic data would be useful so that the models could be validated for chronic exposure. Additional studies designed to define the differences and similarities between 2-butoxyethanol and its acetate with regard to absorption, distribution, metabolism, and excretion would be useful to establish these parameters for 2-butoxyethanol acetate.

Comparative Toxicokinetics. Qualitatively, absorption, metabolism, and excretion appear to be similar in humans and laboratory animals (see discussion above). However, quantitative variations in absorption, metabolism, and excretion of 2-butoxyethanol have been observed with respect to age in rats (Ghanayem et al. 1987a). In addition, the efficiency of absorption of 2-butoxyethanol and excretion of 2-butoxyacetic acid after inhalation exposure differs for several animal species (Carpenter et al. 1956). However, the absorption, distribution, metabolism, and excretion of 2-butoxyethanol after inhalation, oral, and dermal exposure have been studied extensively only in rats. Further studies that focus on the age-related and species-related differences and their implications for human health would be useful. Additionally, *in vitro* studies using human tissue and further research into PBPK modeling in animals would contribute significantly to the understanding of the kinetics of 2-butoxyethanol and would aid in the development of pharmacokinetic models of exposure in humans.

Methods for Reducing Toxic Effects. Development of methods and practices that are specific for 2-butoxyethanol or 2-butoxyethanol acetate would be useful for reducing peak absorption, and body burden, and for interfering with the mechanism of action following 2-butoxyethanol or 2-butoxyethanol acetate exposure. With regard to accidental or intentional poisoning, hemodialysis (Gijsenbergh et al. 1989), gastric lavage, and emesis have been used in the prevention of toxicity (Dean and Krenzelok 1992), and administration of ethanol has been suggested as appropriate therapy (Buckley et al. 1993). Based on animal studies, the administration of inhibitors of alcohol dehydrogenase and aldehyde dehydrogenase may also be appropriate (Ghanayem et al. 1987b). Since 2-butoxyethanol metabolites are thought to play the major role in the toxicity, more information is needed about their interaction with cell membranes and cellular

2. HEALTH EFFECTS

macromolecules. This information would help the development of methods for possible prevention of 2-butoxyethanol-induced toxicity. Special attention should be paid to the production of toxic metabolites, and preferential metabolism to detoxification products.

2.10.3 Ongoing Studies

The open literature contained preliminary reports of ongoing studies in two areas. In an abstract, Raymond et al. (1994) reported immediate and late effects of acute exposure to 2-butoxyethanol in seven clerical workers. Severe, immediate eye and upper respiratory irritation, presyncope, and nausea were observed. Exposure resulted from floor stripping with undiluted 2-butoxyethanol in a small room with little ventilation. The symptoms suggest exposure at 100-300 ppm. All seven workers recovered within several days but noticed skin lesions (cherry angiomas) and recurrent upper respiratory irritation beginning 3 months later. In another preliminary report, the flow properties of rat red blood cells were investigated after oral exposure to 50-500 mg/kg 2-butoxyethanol (Kurantsin-Mills et al. 1992). The physical characteristics of the red blood cells were determined at 0.5, 2, and 4 hours after treatment. Membrane and cellular changes were noted that compromise the flow properties of the cells, thus possibly affecting microcirculation, possibly resulting in hemolysis.

The Chemical Manufacturer's Association is working with the EPA to develop an RfC and an RfD for 2-butoxyethanol. A draft IRIS support document is available (CMA 1997b).

NTP has nearly completed lifetime bioassays of 2-butoxyethanol in mice and rats. The study is undergoing peer review and should provide information on both carcinogenic potential and systemic effects.

No studies regarding the health effects of 2-butoxyethanol or 2-butoxyethanol acetate were reported in the CRISP Data Base of the National Institutes of Health.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of 2-butoxyethanol and 2-butoxyethanol acetate is located in Tables 3-1 and 3-2, respectively.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of 2-butoxyethanol and 2-butoxyethanol acetate is located in Tables 3-3 and 3-4, respectively.

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-1. Chemical Identity of 2-Butoxyethanol

Characteristic	Information	Reference
Chemical name	2-Butoxyethanol	Merck 1989
Synonyms	Ethylene glycol monobutyl ether; ethylene glycol, butyl ether; ethylene glycol mono-n-butyl ether; ethylene glycol n-butyl ether; monobutyl ethylene glycol ether; monobutyl glycol ether; glycol butyl ether; n-butoxyethanol; 2-butoxy-1-ethanol; butoxyethanol; butyl glycol; butyl oxitol; beta-butoxyethanol; 2-butossi-etanol (Italian); 2-butoxy-aethanol (German); butoksyetylowy alkohol (Polish); butylglycol (French, German); Butyl Cellosolve; Butyl Cellu-Sol; Caswell No. 121; Chimec NR Ether; Gafcol EB; Dowanol EB; Poly-Solv EB; Ektasolve EB; Eastman EB	Merck 1989 Weast and Astle 1985 HSDB 1995
Registered trade name	Butyl Cellosolve	Merck 1989
Chemical formula	C ₆ H ₁₄ O ₂	Merck 1989
Chemical structure	CH ₃ -CH ₂ -CH ₂ -CH ₂ -O-CH ₂ -CH ₂ -OH	Weast and Astle 1985
Identification numbers:		
CAS Registry	111-76-2	Weast and Astle 1985
NIOSH RTECS	KJ8575000	HSDB 1995
EPA Hazardous Waste	No data	
OHM/TADS	7216719	HSDB 1995
DOT/UN/NA/IMCO	UN 2369 Ethylene glycol monobutyl ether	HSDB 1995
	IMO 6.1 Ethylene glycol monobutyl ether	
	538	HSDB 1995
HSDB	No data	
NCI	No data	

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-2. Chemical Identity of 2-Butoxyethanol Acetate

Characteristic	Information	Reference
Chemical name	2-Butoxyethanol acetate	Sax 1984
Synonyms	Ethylene glycol monobutyl ether acetate; 2-butoxyethanol acetate; acetic acid, 2-butoxyethyl ester; butoxyethyl acetate; butyl glycol acetate; ethylene glycol butyl ether acetate; glycol monobutyl ether acetate; Butyl Cellosolve acetate; Ektasolve EB acetate; Eastman EB Acetate	HSDB 1995
Registered trade name(s)	No data	
Chemical formula	$C_8H_{16}O_3$	Sax 1984
Chemical structure	$CH_3-CH_2-CH_2-CH_2-O-CH_2-CH_2-O-\overset{\overset{O}{ }}{C}-CH_3$	HSDB 1995
Identification numbers:		
CAS Registry	112-07-2	Sax 1984
NIOSH RTECS	KJ8925000	Sax 1984
EPA Hazardous Waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO	No data	
HSDB	435	HSDB 1995
NCI	No data	

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-3. Physical and Chemical Properties of 2-Butoxyethanol

Property	Information	Reference
Molecular weight	118.17	Merck 1989
Color	Colorless	Marsden and Mann 1963
Physical state	Liquid	Merck 1989
Melting point	-70 °C -75 °C	HSDB 1995 ASTER 1995a
Boiling point	171 °C at 760 mm Hg 50 °C at 4 mm Hg	Weast 1975 Weast 1989
Density at 20°C	0.9019 g/mL	Merck 1989
Odor	Faint odor Mild ethereal odor	Marsden and Mann 1963 ACGIH 1991
Odor threshold:		
Air	0.10 ppm (v/v) 0.4 ppm (v/v)	Amoore and Hautala 1983 OSHA 1990
Water	No data	
Solubility:		
Water at 25 °C	Soluble in all proportions	Riddick and Bunger 1970; Weast 1975
Organic solvent(s)	Miscible with alcohol, ether Soluble in most organic solvents	Weast 1975 Merck 1989
Partition coefficients:		
Log K_{ow}	0.83 0.84	HSDB 1995 ASTER 1995a
Log K_{oc}	1.83 (calculated) 1.79 (calculated)	HSDB 1995; Lyman et al. 1982 ASTER 1995a
Bioconcentration factor		
Log K_{BCF}	0.40 (calculated)	HSDB 1995; Lyman et al. 1982
Vapor pressure		
At 20 °C	0.76 mm Hg	HSDB 1995 OSHA 1990
At 25 °C	0.88 mm Hg	DOW 1993
Henry's law constant (atm·m ³ /mol)	2.08×10 ⁻⁸ (calculated) 5.44×10 ⁻⁶ (calculated)	Howard 1993; HSDB 1995 ASTER 1995a
Vapor-phase rate constant for reaction with photochemically produced hydroxy radicals	1.96×10 ⁻¹¹ cm ³ /molecule-second at 25 °C (estimated)	Atkinson 1987
Atmospheric half-life at 25 °C and 5×10 ⁵ hydroxyl radicals/m ³	17 hours (calculated)	HSDB 1995
Autoignition temperature	238 °C 244 °C	HSDB 1995 Marsden and Mann 1963 ; OSHA 1990

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-3 (continued)

Property	Information	Reference
Flashpoint	60°C (closed cup)	Merck 1989
	62°C (closed cup)	HSDB 1995
	69°C (open cup)	OSHA 1990
	74°C (open cup)	Marsden and Mann 1963
Flammability	May be ignited by heat, sparks, or open flame	HSDB 1995
NFPA Classifications	Health = 2 ^a ; Flammability = 2 ^b ; Reactivity = 0 ^c	HSDB 1995
Conversion factors at 25°C, 1 atm	1 ppm (v/v) = 4.8 mg/m ³	Calculated
	1 mg/m ³ = 0.21 ppm	Calculated
Explosive limits	1.1% (lower);	OSHA 1990
	10.1% (upper)	

^aMaterials hazardous to human health. Areas may be entered freely with full-face mask self-contained breathing apparatus which provides eye protection.

^bMaterials must be moderately heated before ignition will occur. Water spray may be used to extinguish the fire because the material can be cooled below its flashpoint.

^cMaterials that (in themselves) are normally stable even under fire exposure conditions and that are not reactive with water. Normal firefighting procedures may be used.

HSDB = Hazardous Substance Data Bank; NFPA = National Fire Protection Association; OSHA = Occupational Safety and Health Administration; Pa = Pascal (133 Pa = 1 mm Hg)

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-4. Physical and Chemical Properties of 2-Butoxyethanol Acetate

Property	Information	Reference
Molecular weight	160.24	Sax 1984
Color	Colorless	Verschueren 1983
Physical state	Liquid	Verschueren 1983
Melting point	-63.5°C	Sax 1984
Boiling point	192.3°C	Verschueren 1983
Density at 20°C	0.94 g/mL	Verschueren 1983
Odor	Fruity	Verschueren 1983
Odor threshold:		
Air	0.1 ppm (absolute threshold)	Verschueren 1983
	0.35-0.48 ppm (recognition)	Verschueren 1983
Water	No data	
Solubility:		
Fresh water at 20 °C	11 g/L 1 g/100 g	HSDB 1995 OSHA 1990
Organic solvent(s)	Soluble in hydrocarbons and organic solvents	OSHA 1990
Partition coefficients:		
Log K _{ow}	1.71	ASTER 1995b
Log K _{oc}	1.41 (calculated)	HSDB 1995
	2.27 (calculated)	ASTER 1995b
Bioconcentration factor (log K _{BCF})	0.51 (calculated)	HSDB 1995
Vapor pressure at 20°C	0.375 mm Hg 0.579 mm Hg (calculated)	HSDB 1995 ASTER 1995b
Henry's law constant (atm·m ³ /mol)	7.19×10 ⁻⁶ (calculated) 1.56×10 ⁻⁵	Howard 1993; HSDB 1995 ASTER 1995b
Vapor-phase rate constant with photochemically produced hydroxyl radicals	20.9×10 ⁻¹² cm ³ /molecule-second at room temperature (calculated)	Atkinson 1987; HSDB 1995
Atmospheric half-life at 25°C and 5×10 ⁵ hydroxy radicals/m ³	18.4 hours (calculated)	Atkinson 1987; HSDB 1995
Hydrolysis half-life	>1,000 days	ASTER 1995b
Autoignition temperature	340°C	OSHA 1990

3. CHEMICAL AND PHYSICAL INFORMATION

Table 3-4 (continued)

Property	Information	Reference
Flashpoint	73.9°C (closed cup)	OSHA 1990
	87.8°C (open cup)	OSHA 1990
Flammability	Moderate fire hazard when exposed to heat, flame, or oxidizers	HSDB 1995
NFPA Classifications	Health = 1 ^a	HSDB 1995
	Flammability = 2 ^b	HSDB 1995
	Reactivity = 0 ^c	HSDB 1995
Conversion factors at 25°C and 1 atm	1 ppm (v/v) = 6.54 mg/m ³	HSDB 1995
	1 mg/m ³ = 0.157 ppm	HSDB 1995
Explosive limits	0.88% at 93°C lower; 8.54% at 135°C upper	HSDB 1995

^aMaterials only slightly hazardous to health. It may be desirable to wear self-contained breathing apparatus.

^bMaterials that must be moderately heated before ignition will occur. Water spray may be used to extinguish fire because material can be cooled below its flashpoint.

^cMaterials that (in themselves) are normally stable even under fire exposure conditions and that are not reactive with water. Normal firefighting procedures may be used.

NFPA = National Fire Protection Association

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Glycol ethers consist of a large group of organic solvents that are widely used in formulating cleaning products and protective coatings (Browning and Curry 1994; Rowe and Wolf 1982; Vincent et al. 1993). 2-Butoxy-ethanol, one of the simplest glycol monoalkyl ethers, is commonly encountered and massively produced for use in several industries (Dow 1993; Gibson 1984; Rowe and Wolf 1982). Approximately 130 million pounds of 2-butoxyethanol were produced in the United States in both 1972 and 1975 (HSDB 1997). Data on production volumes between 1975 and 1983 were not found. However, there was a significant overall increase in production during that period, with 2-butoxyethanol being the largest volume glycol ether produced in 1983 (HSDB 1997); reportedly more than 230 million pounds were produced (Gibson 1984 as cited in Ghanayem et al. 1987b). Domestic production of 2-butoxyethanol reached 271 million pounds in 1984 (HSDB 1997) and increased to over 300 million pounds in 1986 (NIOSH 1990). A production volume of 408.5 million pounds of 2-butoxyethanol has been estimated for 1995 (CMA 1997a). Significantly lower and relatively constant production of 2-butoxyethanol acetate was reported for the period 1972-1977, with production volumes in 1972, 1975, and 1977 of 13.4 million pounds, 11 million pounds, and 11 million pounds, respectively (NIOSH 1990). More recent production data for 2-butoxyethanol acetate could not be found in the available literature.

Major producers of 2-butoxyethanol are Dow Chemical, USA (Midland, Michigan); Eastman Chemical Co., Texas Eastman Co. Division (Longview, Texas); Occidental Petroleum Corporation, Oxy Petrochemicals, Inc. (Dallas, Texas); Shell Chemical Co. (Geismar, Louisiana); and Union Carbide Corporation, Solvents and Intermediates (Seadrift, Texas) (HSDB 1997; SRI 1997; USITC 1992). The Occidental Petroleum Corporation and the Tennessee Eastman Division of the Eastman Chemical Co. (Kingsport, Tennessee) are major producers of 2-butoxyethanol acetate (HSDB 1997; SRI 1997). Recent data showing the combined production volume of 2-butoxyethanol acetate for these producers were not located. Both compounds are included in the reports of the Toxics Release Inventory (TRI) database (EPA 1995) as part of the required generic reporting of all ethylene glycol ethers. Therefore, information pertaining to the releases of the individual compounds to the environment are not available.

Ethylene glycol monoalkyl ethers are not manufactured as pure compounds but must be separated from the diethers and higher glycols (NTP 1993; NIOSH 1990). There are two common methods of producing

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

2-butoxyethanol: reaction of ethylene oxide with anhydrous butyl alcohol in the presence of a catalyst and direct alkylation of ethylene chlorohydrin or ethylene glycol using sodium hydroxide and an alkylating agent such as dibutyl sulfate (HSDB 1997; NOSH 1990; Rowe and Wolf 1982). By far the dominant method of 2-butoxyethanol production is treatment of butyl alcohol with ethylene oxide. Information on older products indicates that there may be a considerable difference in the purity of 2-butoxyethanol manufactured in the United States, particularly between industrial and technical formulations. Depending on the production process, manufacturer, and chemical grade of the material, 2-butoxyethanol may contain impurities such as sodium hydroxide (caustic), ethylene glycol, diethylene glycol, and diethylene glycol monobutyl ether (Dow 1958; Eastman Kodak 1988). Dowanol EB Crude, an industrial formulation, was reported to contain 0.25% sodium hydroxide (caustic) (Dow 1958). Ektasolve, a technical grade formulation with >99% purity, was reported to contain 0.2% (w/w) each of ethylene glycol, diethylene glycol, and diethylene glycol monobutyl ether (Eastman Kodak 1988). Total impurity levels in 2-butoxyethanol from different manufacturers have been reported to range from ppm levels to 1-2% (w/w) (Dow 1972; Eastman Kodak 1983,1988).

2-Butoxyethanol acetate is predominantly produced by treatment of 2-butoxyethanol with acetic acid. Treatment with acetic acid anhydride or acetic acid chloride are secondary, minor methods of production.

4.2 IMPORT/EXPORT

The most recent import and export data found for 2-butoxyethanol indicate that imports into the United States increased significantly from a negligible amount in 1972 to 89,000 pounds in 1984 (HSDB 1997). Export volumes also increased significantly from 9 million pounds in 1972, to 12 million pounds in 1975, to 71 million pounds in 1984 (HSDB 1997). No quantitative import or export data were found in the available literature for 2-butoxyethanol acetate. The National Trade Data Bank (NTDB 1997) reports import/export data for monobutyl ethers of mono or di-ethylene glycols rather than specific data for 2-butoxyethanol or 2-butoxyethanol acetate.

4.3 USE

2-Butoxyethanol is used extensively in the production of cleaning agents and as a general solvent because it exhibits properties of both alcohols and ethers (Gibson 1984 as cited in Ghanayem et al. 1987b). It is used in formulating industrial and household cleaners, metal cleaners, silicone caulks, and protective surface coatings such as spray lacquers, quick-dry lacquers, enamels, varnishes, and latex paints (Dow 1993; HSDB 1997; Lewis 1993; NIOSH 1990; Rempel et al. 1991; Tichenor and Mason 1988; Vincent et al. 1993). It is also

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

used in inks, degreasers, paint thinners, and paint stripping formulations (Hahn and Werschulz 1986; Lehmann et al. 1986; Yamano et al. 1991). 2-butoxyethanol has optimum properties (i.e., well-balanced distribution of hydrophilic and hydrophobic groups, complete miscibility with water at room temperature, and an appropriate rate of evaporation) for the production, storage, and application of aqueous coating systems (Appelt 1990). 2-Butoxyethanol is also a component of dry-cleaning compounds (Lewis 1993). In the textile industry, 2-butoxyethanol is used as a dye component to prevent spotting during fabric printing and dyeing (HSDB 1997; Lewis 1993). 2-Butoxyethanol is also used in liquid soaps and cosmetics (Rowe and Wolf 1982). Based on information provided to the IDA, 2-butoxyethanol was found in 111 cosmetic products in 1994 at concentrations up to 10% (Cosmetic Ingredient Review Expert Panel 1996). The emulsifying properties of soap are improved when 2-butoxyethanol is included in the formulation as a mutual solvent for “soluble” mineral oils (Lewis 1993). Functioning as a coupling agent, the compound stabilizes immiscible ingredients in metal cleaning products, textile lubricants, hydraulic fluids, cutting oils, and liquid household cleaning products (HSDB 1997; NIOSH 1990; Rowe and Wolf 1982; Vincent et al. 1993). 2-Butoxyethanol is used as a chemical intermediate in the synthesis of acetate esters as well as phthalate and stearate plasticizers (Dow 1993; HSDB 1997); it is also used as a component of some adhesives (FDA 1993a). In 1972, the use pattern for 2-butoxyethanol was as follows: solvent for protective coatings, 41%; other solvent uses, 3 1%; solvent for metal cleaners and liquid household cleaners, 18%; synthesis of 2-butoxyethanol acetate, 9%; and synthesis of di(2-butoxyethyl) phthalate, 1% (HSDB 1997). The pattern for consumption in 1984, which did not include household cleaners was as follows: coatings solvents, 65%; intermediates, 20%; and miscellaneous solvents, 15% (HSDB 1997). Minor applications include the use of 2-butoxyethanol as a solvent or co-solvent in pesticide formulations (Dow 1993; Leaf 1985 as cited in NIOSH 1990) and automotive brake fluids (Leaf 1985 as cited in NIOSH 1990). Nearly half of the more than 740 products containing 2-butoxyethanol marketed in the United States in 1977 were intended for household use; the average concentration of 2-butoxyethanol in these household products was 2.8% (Consumer Products Safety Commission 1977). The concentration of 2-butoxyethanol used in industrial and household window cleaning agents has been found to range from 1% to 30% by volume (Vincent et al. 1993).

2-Butoxyethanol acetate is primarily used as a high-boiling, retarder solvent (i.e., an active, slow-evaporating solvent which ensures smooth film formation) for nitrocellulose lacquers, acrylic enamels, epoxy resins, and multicolor lacquers (Leaf 1985 as cited in NIOSH 1990; Lewis 1993). 2-Butoxyethanol acetate is also a film-coalescing aid for polyvinyl acetate latex and is used in some ink and spot remover formulations (Leaf 1985 as cited in NIOSH 1990; Lewis 1993). In addition, the chemical is used in inks, degreasers, paints, and paint thinner formulations (Lehman et al. 1986) and as a component of some adhesives (FDA 1993a). The

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

concentration of 2-butoxyethanol acetate as a retarder solvent in coating formulations is generally 1-5% by volume (Leaf 1985 as cited in NIOSH 1990). Current information on the use pattern for 2-butoxyethanol was not located in the available literature.

4.4 DISPOSAL

Regulations governing the treatment and disposal of wastes containing 2-butoxyethanol or 2-butoxyethanol acetate are detailed in Chapter 7. A recommended method of disposal for small amounts of 2-butoxyethanol involves mixing the compound with more flammable solvents to improve combustion, and then atomizing the mixture in an incinerator (IRPTC 1985). In a preliminary investigation of the photodegradation of 2-butoxyethanol, Minero et al. (1989) concluded that in the presence of semiconductor particles (titanium dioxide [TiO_2]), degradation is very rapid and effective. A quantitative formation of carbon dioxide was observed. Their investigation also concluded that under the proper conditions, an iodine-doped organic polymer (polyphenylacetylene) can catalyze 70-100% photooxidation of 2-butoxyethanol (Minero et al. 1989). No data were found in the available literature on the amounts of 2-butoxyethanol or 2-butoxyethanol acetate disposed of in the United States.

5. POTENTIAL FOR HUMAN EXPOSURE

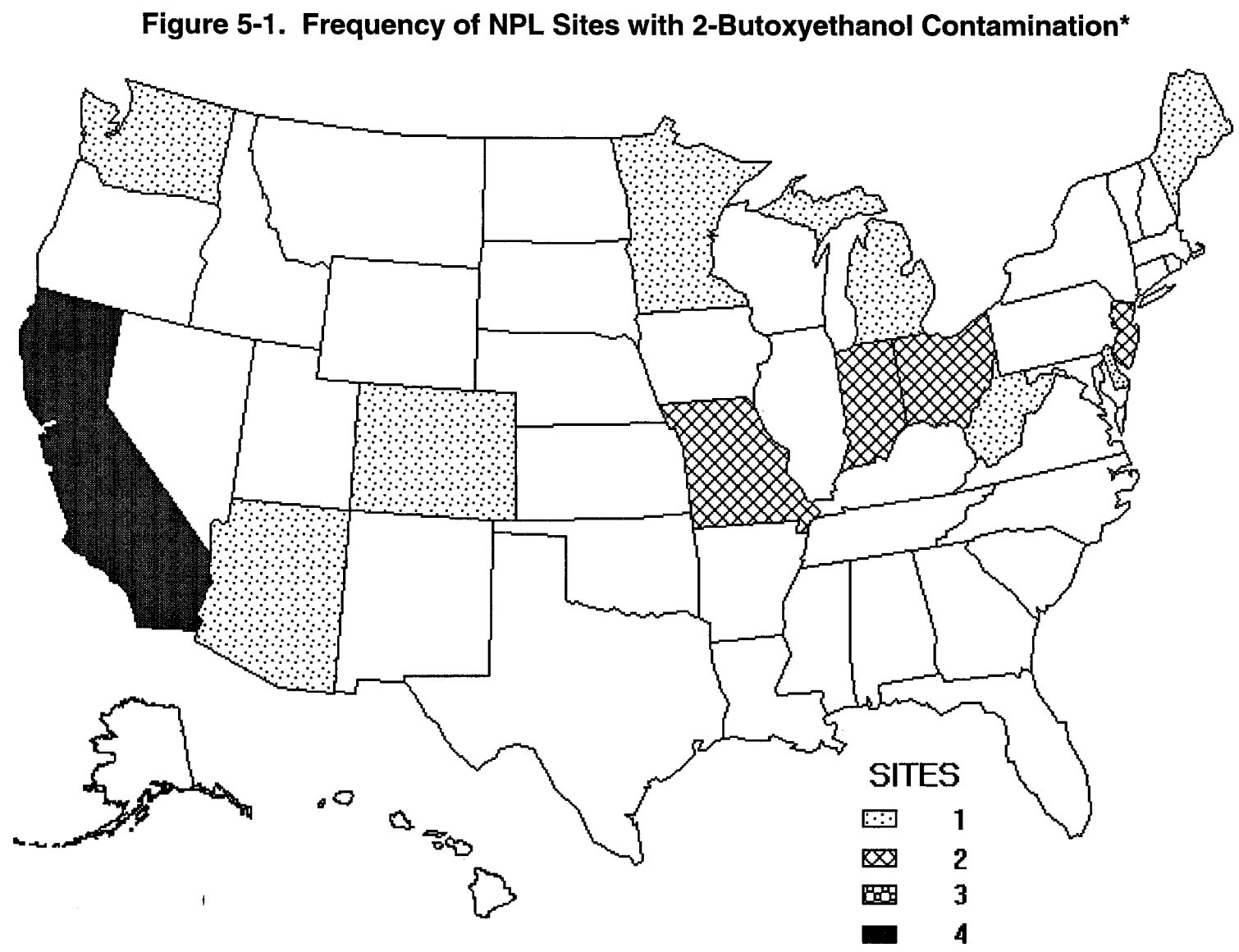
5.1 OVERVIEW

2-Butoxyethanol has been identified in at least 20 of the 1,430 current or former EPA NPL hazardous wastes sites (HazDat 1996). However, the number of sites evaluated for 2-butoxyethanol is not known. The frequency of these sites within the United States can be seen in Figure 5-1.

2-Butoxyethanol acetate has not been identified in any of the 1,430 current or former EPA NPL hazardous wastes sites (HazDat 1996). However, the number of sites evaluated for 2-butoxyethanol acetate is not known.

2-Butoxyethanol and 2-butoxyethanol acetate do not occur naturally. Little quantitative information was found in the available literature characterizing the release of these chemicals to the environment. 2-Butoxyethanol and 2-butoxyethanol acetate may be released to air, water, or soil from facilities where they are manufactured or processed. However, information about the release of 2-butoxyethanol is not available in the TRI database because the database contains such information only for the general toxic chemical category of glycol ethers and not for specific glycol ethers (EPA 1995). No information is available in the TRI database on the amount of 2-butoxyethanol acetate released to air, water, or soil by facilities that manufacture or process this compound because this compound is not included under SARA, Title III, and therefore, is not among the chemicals that facilities are required to report (EPA 1995).

2-Butoxyethanol and 2-butoxyethanol acetate may also be released to the environment from facilities that use these chemicals in the production of other materials, including resins, lacquers, varnishes, enamels, dry-cleaning compounds, soap, emulsifying agents, inks, and (to a minor extent) herbicides. These chemicals may also be directly released to the atmosphere by evaporation during the use of these products in occupational or household settings. There is a potential for atmospheric release of 2-butoxyethanol and 2-butoxyethanol acetate from hazardous waste sites; however, no data were found in the available literature. 2-Butoxyethanol is released to water via leachates from municipal landfills and hazardous waste sites (Dunlap et al. 1976a, 1976b; Stonebreaker and Smith 1980). It has been detected in surface water samples at 2 of the 20 NPL sites and in groundwater in samples at 7 of the 20 NPL sites where 2-butoxyethanol has been detected in some environmental media (HazDat 1996). It may also be directly released to air, soil, and plants during application of herbicides that contain this chemical and to surface water when sprayed in excessive amounts or drift occurs



*Derived from HazDat 1997

5. POTENTIAL FOR HUMAN EXPOSURE

(Dow 1993). 2-Butoxyethanol is also released to soil at hazardous waste sites. It has been detected in the soil samples at 3 of the 20 NPL sites and in sediment samples at 1 of the 20 NPL sites where this compound has been found in some environmental media (HazDat 1996). No information was found on detection of 2-butoxyethanol acetate in surface water, groundwater, or soil at any NPL hazardous waste sites.

Information on the transport and partitioning of 2-butoxyethanol and 2-butoxyethanol acetate is derived primarily from their physical and chemical properties (see Table 3-3 and 3-4). Any 2-butoxyethanol or 2-butoxyethanol acetate in the atmosphere would be almost exclusively in the vapor phase (Eisenreich et al. 1981). They may be partitioned to soil and water by wet or dry deposition, with wet deposition predominating. Because of the relatively short atmospheric half-lives (<1 day) of these chemicals, they are not transported long distances in the atmosphere (Grosjean 1990; Howard 1993). Both 2-butoxyethanol and 2-butoxyethanol acetate volatilize only slowly from water, with the rate of volatilization somewhat slower for 2-butoxyethanol (Thomas 1990). These compounds remain in water primarily in the dissolved state with very little partitioning to suspended solids and sediment; the amount removed by sorption is somewhat higher for 2-butoxyethanol acetate than for 2-butoxyethanol (Swann et al. 1983). Based on bioconcentration factors (BCFs) estimated from quantitative structure-activity relationships (ASTER 1995a, 1995b), bioconcentration in aquatic organisms is not a significant process for either 2-butoxyethanol or 2-butoxyethanol acetate. Neither compound is expected to biomagnify in the food chain. The partitioning of 2-butoxyethanol and 2-butoxyethanol acetate from moist and dry soil to the atmosphere by volatilization is negligible. Both compounds are mobile in soil and leach to groundwater, with 2-butoxyethanol expected to leach more readily than 2-butoxyethanol acetate (Swann et al. 1983).

The most significant chemical reaction of 2-butoxyethanol or 2-butoxyethanol acetate in air is with photochemically generated hydroxyl radicals. Estimated atmospheric half-life values for 2-butoxyethanol range from 3.28 to 32.8 hours (Grosjean 1990; Howard et al. 1991). The atmospheric half-life value for 2-butoxyethanol acetate has been estimated to be approximately 18 hours (Grosjean 1990). The products of reaction of 2-butoxyethanol and 2-butoxyethanol acetate with hydroxyl radicals have not been identified. Neither photolysis nor reaction with ozone or nitrate radicals is an important atmospheric transformation process for these compounds (Grosjean 1990; Howard 1993). Aerobic biodegradation appears to be the most important transformation process for both 2-butoxyethanol and 2-butoxyethanol acetate in water (Dow 1993; Price et al. 1974; Waggy et al. 1994; Zahn and Wellens 1980), with the biodegradation half-life of 2-butoxyethanol in natural bodies of surface waters estimated to be in the range of 7-28 days (Howard et al. 1991). The intermediate products of aerobic biodegradation of 2-butoxyethanol and 2-butoxyethanol acetate have not

5. POTENTIAL FOR HUMAN EXPOSURE

been identified. However, by analogy with enzymatic degradation products found in human and animal studies, both compounds may be degraded to carbon dioxide and water via 2-butoxyacetic acid (Ghanayem et al. 1987c; Johanson et al. 1988). Neither direct photolysis nor hydrolysis is an important transformation process for these compounds in water (ASTER 1995a, 1995b; Harris 1990; Howard 1993). Because fugacity models predict that <1% of these compounds will partition into soil (ASTER 1995a, 1995b), little research has been conducted to determine their fate in this medium. By analogy with the fate of 2-butoxyethanol and 2-butoxyethanol acetate in water, it is possible that aerobic biodegradation may be the most important transformation process for these compounds in soil and sediment, with the rate of aerobic biodegradation decreasing with increasing depth (i.e., decreasing availability of oxygen). Consequently, both compounds may persist longer in deeper soils and sediments.

Except for occupational settings, data on levels of 2-butoxyethanol or 2-butoxyethanol acetate in the environment are very limited. Little information was found in the available literature on concentrations of 2-butoxyethanol in ambient air, surface water, sediment, or soil in the United States. In indoor air, 2-butoxyethanol has been found at an average concentration of 0.214 ppb volume per volume (v/v) ($1.03 \text{ c(g/ m}^3\text{)}$) (Shah and Heyderdahl 1988; Shah and Singh 1988). 2-Butoxyethanol has been found at a concentration of 23 $\mu\text{g/L}$ in one surface water sample collected near the Valley of the Drums, Kentucky (Stonebreaker and Smith 1980). 2-Butoxyethanol has also been detected in one groundwater sample collected beneath a municipal landfill; however, the concentration was not reported (Dunlap et al. 1976a, 1976b). 2-Butoxyethanol has also been found in drinking water in six U.S. cities and in finished water from advanced waste treatment plants in six U.S. cities; however, no concentrations were reported (Lucas 1984). In other environmental media, 2-butoxyethanol has been found in waste water effluents at concentrations up to 100 $\mu\text{g/L}$ (Jungclaus et al. 1976). No information was found in the available literature on concentrations of 2-butoxyethanol acetate in ambient or indoor air; surface water, groundwater, or drinking water; or sediment or soil. There may be a potential for contamination of food with 2-butoxyethanol and 2-butoxyethanol acetate from labeling and packaging materials or processing activities (FDA 1993a, 1993b, 1993c) or from the minor use of herbicides containing 2-butoxyethanol (Dow 1993; Leaf 1985 as cited in NIOSH 1990); however, no information was found in the available literature on detection of these compounds in food. It should be noted that the amounts of 2-butoxyethanol and 2-butoxyethanol acetate found by chemical analysis are not necessarily the amounts that are bioavailable.

The general population is exposed to 2-butoxyethanol and 2-butoxyethanol acetate primarily via inhalation or dermal absorption during use of common household products containing this compound as a solvent (see

5. POTENTIAL FOR HUMAN EXPOSURE

Section 4.3). Non-occupational exposures to 2-butoxyethanol may also occur via ingestion of contaminated drinking water supplies (Lucas 1984).

Occupational exposures to 2-butoxyethanol and 2-butoxyethanol acetate also occur primarily via inhalation or dermal absorption. Estimates from the National Occupational Exposure Survey (NOES) conducted by the National Institute of Occupational Safety and Health (NIOSH) indicate that from 1981 to 1983 more than 2 million workers were potentially exposed to 2-butoxyethanol, and more than 150,000 workers were potentially exposed to 2-butoxyethanol acetate (NIOSH 1989b). In addition to occupational exposures related to the production, processing, or handling of these chemicals, workers may be exposed to 2-butoxyethanol and 2-butoxyethanol acetate in a wide variety of occupations in which products containing these compounds are used. These occupations include janitors and cleaners, painters, mechanics, nurses and health aids, construction workers, printing machine operators, and furniture and wood finishers.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

2-Butoxyethanol may be released to the atmosphere via emissions or effluents at sites where it is manufactured, processed, or used in the production of a wide variety of other materials (see Sections 4.1 and 4.3). These products include nitrocellulose resins, spray and quick drying paints and lacquers, varnishes, enamels, dry cleaning compounds, varnish and textile spot removers (in printing and dyeing), soap solutions, cosmetics, window cleaning agents, and emulsifying agents (Appelt 1990; Lewis 1993; NIOSH 1990; Rowe and Wolf 1982; Vincent et al. 1993); silicone caulk (Tichenor and Mason 1988); and herbicides (Dow 1993; BPA 1993b; Leaf 1985 as cited in NIOSH 1990). 2-Butoxyethanol may also be directly released to the atmosphere by evaporation during the use of these products.

Similarly, 2-butoxyethanol acetate may be released to the atmosphere via emissions or effluents at sites where it is manufactured, processed, or used in the production of paints, lacquers, thinners, inks, resins, and other materials (Lewis 1993; NIOSH 1990) (see Sections 4.1 and 4.3). It may also be directly released to the atmosphere by evaporation during the use of these products. The atmospheric emission rate of 2-butoxyethanol acetate (Butyl Cellosolve® acetate) from painting operations at a Janesville, Wisconsin, automobile assembly facility was estimated at 13.3 liters/hour (3.5 gallons/hour) (Sexton and Westberg 1980).

5. POTENTIAL FOR HUMAN EXPOSURE

No information is available in the TRI database on the amount of 2-butoxyethanol released to the atmosphere by facilities that manufacture or process this compound because the database contains such information only for the general toxic chemical category of glycol ethers and not for specific glycol ethers (EPA 1995). No information is available in the TRI database on the amount of 2-butoxyethanol acetate released to the atmosphere by facilities that manufacture or process this compound because this compound is not included under SARA, Title III; it is therefore not among the chemicals that facilities are required to report (EPA 1995).

There is a potential for atmospheric release of 2-butoxyethanol and 2-butoxyethanol acetate from hazardous waste sites. However, no information was found on detection of these chemicals in air at any NPL hazardous waste sites (HazDat 1996).

5.2.2 Water

2-Butoxyethanol and 2-butoxyethanol acetate may be released to water by facilities that manufacture, process, or use these compounds in the production of other materials (see Sections 4.1 and 4.3). Information on releases to water from facilities that manufacture or process 2-butoxyethanol is not available in the TRI database because the database contains such information only for the general toxic chemical category of glycol ethers and not for specific glycol ethers (EPA 1995). No information is available in the TRI database on the amount of 2-butoxyethanol acetate released to water by facilities that manufacture or process this compound because this compound is not included under SARA, Title III; it is therefore not among the chemicals that facilities are required to report (EPA 1995).

2-Butoxyethanol may be released to water in leachates from municipal landfills and hazardous waste sites (Dunlap et al. 1976a, 1976b; Stonebreaker and Smith 1980). 2-Butoxyethanol has been detected in surface water samples at 2 of the 20 NPL sites and in groundwater samples at 7 of the 20 NPL sites where 2-butoxy-ethanol has been detected in some environmental medium (HazDat 1996). No information was found on detection of 2-butoxyethanol acetate in surface water or groundwater at any NPL hazardous waste sites (HazDat 1996).

2-Butoxyethanol may also be directly released to surface water when excessive amounts are sprayed or drift occurs during application of herbicides that contain this compound (Dow 1993). Direct release of 2-butoxyethanol to surface water may also occur during outdoor use of consumer products that contain this chemical (e.g., liquid cleaners, varnishes, paints); however, these releases are not expected to be significant.

5. POTENTIAL FOR HUMAN EXPOSURE

5.2.3 Soil

2-Butoxyethanol and 2-butoxyethanol acetate may be released to soil by facilities that manufacture, process, or use these compounds in the production of other materials (see Sections 4.1 and 4.3). Information on releases to soil from facilities that manufacture or process 2-butoxyethanol is not available in the TRI database because the database contains such information only for the general toxic chemical category of glycol ethers and not for specific glycol ethers (EPA 1995). No information is available in the TRI database on the amount of 2-butoxyethanol acetate released to soil by facilities that manufacture or process this compound because this compound is not included under SARA, Title III and therefore, is not among the chemicals that facilities are required to report (EPA 1995).

2-Butoxyethanol and 2-butoxyethanol acetate may also be released to the soil and sediment at hazardous waste sites. 2-Butoxyethanol has been detected in soil samples at 3 of the 20 NPL sites and in sediment samples at 1 of the 20 NPL sites where this compound has been found in some environmental medium (HazDat 1996). No information was found on detection of 2-butoxyethanol acetate in soil or sediment at any NPL hazardous waste sites (HazDat 1996).

2-Butoxyethanol may also be directly released to soil during application of herbicides that contain this compound (Dow 1993). Direct release of 2-butoxyethanol to soil may also occur during outdoor use of consumer products that contain this chemical (e.g., liquid cleaners, varnishes, paints); however, these releases are not expected to be significant.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The vapor pressure of 2-butoxyethanol is 0.76 mm Hg at 20°C (HSDB 1995; Lewis 1993) and 0.88 mm Hg at 25°C (Dow 1993). The vapor pressure of the acetate is 0.375 mm Hg at 20°C (HSDB 1995; Weber et al. 1981). Based on these vapor pressures, both compounds would be present almost exclusively in the vapor phase in the atmosphere (Eisenreich et al. 1981). Compounds in the vapor phase are transported from the atmosphere to land and water by both wet deposition (via rain and snow scavenging) and dry deposition (via vapor exchange across the water and soil surfaces during impaction) (Bidleman 1988). Physical transport by wet deposition of both compounds is more important than transport arising from dry deposition since both

5. POTENTIAL FOR HUMAN EXPOSURE

compounds are water soluble. The rate of transport of the compounds from one point to another point in the atmosphere will determine their ability to participate in long-distance transport. The longer the persistence time (or half-life) of a chemical in the atmosphere, the farther it is transported in air. The half-life of both chemicals is <1 day (see Section 5.3.2.1), indicating that neither is transported long distances in the air.

The unitless air/water partition coefficient or Henry's law constant (H) for 2-butoxyethanol in a 0.3M sodium chloride solution is 1.42×10^{-4} at 37°C (Johanson and Dynesius 1988). Conversion of this unitless value to the units commonly used for H (Thomas 1990) gives a value of 3.61×10^{-6} atm- m³/mol. Other values ranging from 2.08×10^{-8} (HSDB 1995; SRC 1994) to 5.44×10^{-6} atm- m³/mol (ASTER 1995a) for 2-butoxyethanol in water at 25 °C have been estimated. Values of H ranging from 6.74×10^{-7} to 1.56×10^{-5} atm- m³/mol (ASTER 1995b; Howard 1993; SRC 1994) have been estimated for 2-butoxyethanol acetate. Based on volatility characteristics associated with H (Thomas 1990), the volatilization of both compounds from water is slow, with the volatility of 2-butoxyethanol being somewhat less than that of the acetate. Based on estimated K_{oc} values of 62 and 186 for 2-butoxyethanol and 2-butoxyethanol acetate, respectively (ASTER 1995a, 1995b), the concentrations of both compounds are expected to be higher in water primarily in the dissolved state. Very little would be expected to partition into suspended solids and sediment in water, although 2-butoxyethanol acetate would be adsorbed to suspended solids and sediment to a greater extent than would 2-butoxyethanol (Swarm et al. 1983).

From quantitative structure-activity relationships, the bioconcentration factors (BCFs) for 2-butoxyethanol and 2-butoxyethanol acetate in fathead minnows (*Pimephales promelas*) have been estimated to be 2 and 9, respectively (ASTER 1995a, 1995b). Therefore, bioconcentration of either compound in aquatic organisms is not important. No information was located that would suggest that either compound biomagnifies in the food chain. This is not surprising, considering that the low K_{ow} values (see Tables 3-3 and 3-4) indicate low probability of lipid uptake.

Mackay Level 1 modeling was used to estimate the distribution of 2-butoxyethanol in various environmental compartments (air, soil, water, biota, suspended solids, sediment) (Staples 1997). The model uses physical properties (aqueous solubility, vapor pressure, soil and sediment distribution coefficient, biota concentration factor) and the assumption that environmental compartments are approximately proportional in size to the natural environment. The model calculates the general distribution of 2-butoxyethanol following the release of 100 moles. The model estimated that at equilibrium about 96% of the 2-butoxyethanol would be found in

5. POTENTIAL FOR HUMAN EXPOSURE

water, with <0.1%, 2%, <0.1 %, <0.1 %, and 2% found in air, soil, biota, suspended solids, and sediment, respectively.

The transport of the two compounds from moist and dry soil to air via volatilization is negligible because of the low values for Henry's law constant and vapor pressure. The estimated K_{oc} values of 62 and 186 for 2-butoxyethanol and 2-butoxyethanol acetate, respectively (ASTER 1995a, 1995b), suggest that both compounds would be mobile in soils and would leach from soil to groundwater, although the leachability of 2-butoxyethanol is higher than that of 2-butoxyethanol acetate (Swann et al. 1983).

5.3.2 Transformation and Degradation

5.3.2.1 Air

The direct photolysis of 2-butoxyethanol in the atmosphere is not important since it does not absorb sunlight available in the troposphere (Howard 1993; Silverstein and Bassler 1963). The reactivity of 2-butoxyethanol with three important atmospheric reactants produced by photochemical reactions was estimated from structure-reactivity relationships (Grosjean 1990). The rates of reaction of 2-butoxyethanol with ozone and nitrate radicals were estimated to be too slow to be important (Grosjean 1990). The reactions of ozone and nitrate radicals with 2-butoxyethanol acetate, will also be negligible. The rate constant for reaction of 2-butoxyethanol with hydroxyl radicals has been estimated to range from 2.1 to 2.3×10^{-11} $\text{cm}^3/\text{molecule}\cdot\text{set}$ (Grosjean 1990; SRC 1995). If the average concentration of hydroxyl radicals during a 24-hour day is assumed to be 5×10^5 $\text{molecules}/\text{cm}^3$, the half-life (first order kinetics) for 2-butoxyethanol can be estimated to range from approximately 3.28 to 32.8 hours (Grosjean 1990; Howard et al. 1991; Lyman 1990; SRC 1995). Therefore, 2-butoxyethanol does not persist in the atmosphere. Based on a structure-reactivity relationship method (Atkinson 1987), the rate constant for the reaction of 2-butoxyethanol acetate with hydroxyl radicals in the atmosphere was estimated to be 2.1×10^{-11} $\text{cm}^3/\text{molecule}\cdot\text{set}$ (Howard 1993; SRC 1995). Assuming an average (24-hour) day hydroxyl radical concentration of 5×10^5 $\text{molecules}/\text{cm}^3$, the half-life (first order kinetics) for this reaction is approximately 18 hours (Grosjean 1990; Lyman 1990; SRC 1995). Therefore, 2-butoxyethanol acetate also does not persist in the atmosphere. The products of reaction of 2-butoxyethanol and 2-butoxyethanol acetate with hydroxyl radicals have not been identified.

5. POTENTIAL FOR HUMAN EXPOSURE

5.3.2.2 Water

Functional groups in both alcohols and ethers are generally resistant to hydrolysis (Harris 1990). Therefore, hydrolysis of 2-butoxyethanol, which contains both alcohol and ether functional groups, is not expected. The estimated hydrolysis half-life (first order kinetics) for 2-butoxyethanol acetate of >1,000 days (ASTER 1995a) indicates that the hydrolysis of 2-butoxyethanol acetate in water is also not expected. 2-Butoxyethanol does not absorb light of wavelength >290 nm (Silverstein and Bassler 1963). Therefore, photolysis of this compound by absorption of sunlight is not important. Aerobic biodegradation screening studies with filtered sewage for inocula and theoretical biological oxygen demand (BODT) as a measure of complete biodegradation (mineralization of the compound to carbon dioxide and water) indicated 5% mineralization of 2-butoxyethanol in 5 days (Dow 1993), 57-74% in 10 days (Dow 1993; Price et al. 1974), and 72-88% in 20 days (Dow 1993; Price et al. 1974). The Organization for Economic Cooperation and Development (OECD) recommends a closed bottle biodegradation test with settled sewage as microbial inoculum for determining the biodegradation potential of organic chemicals. The biodegradation of 2-butoxyethanol was determined using the OECD test procedure, to be 47% in 5 days, 70% in 15 days, and 75% in 28 days (Waggy et al. 1994). Thus, the tests used both in the United States and in Europe to determine the biodegradation potential of organic chemicals indicate that 2-butoxyethanol is readily biodegradable. The aerobic biodegradation half-life (first order kinetics) of 2-butoxyethanol in natural bodies of surface water has been estimated to be in the range of 7-28 days, compared to an estimated aqueous anaerobic biodegradation half-life (first order kinetics) ranging from 28 days to 16 weeks (Howard et al. 1991). Hydrolysis is not likely to be an important transformation mechanism for 2-butoxyethanol (ATSDR 1995b). The biodegradation half-life (first order kinetics) of 2-butoxyethanol in groundwater has been estimated to range from 14 days to 8 weeks, based on the estimated aerobic biodegradation (unacclimated aqueous) half-life for this compound (Howard et al. 1991). The intermediate products of aerobic biodegradation of 2-butoxyethanol were not identified in any of the screening tests. However, as observed in human and animal studies (Johanson et al. 1989), 2-butoxy-ethanol acetate may enzymatically hydrolyze to 2-butoxyethanol and acetic acid as a result of biodegradation. By analogy to animal metabolism (Ghanayem et al. 1987c) it is possible that any 2-butoxyethanol formed may undergo further enzymatic oxidation (e.g., via dehydrogenase) to the butoxyacetaldehyde and finally to 2-butoxyacetic acid before being degraded to carbon dioxide and water.

Biodegradation studies were conducted using the Zahn-Wellens screening test (a batch method in which biodegradation by activated sludge is determined indirectly by measurement of chemical oxygen demand and/or dissolved organic carbon removal). This study indicated that under the test conditions, the

5. POTENTIAL FOR HUMAN EXPOSURE

biodegradation of 2-butoxyethanol acetate was 90% within 6.5 days, with a degradation rate of 12% per day as determined by measurement of chemical oxygen demand (Zahn and Wellens 1980). No lag period was observed for onset of biodegradation in the Zahn-Wellens test. Therefore, the acetate will biodegrade easily in natural bodies of surface water, but no estimate of biodegradation half-life was located in the literature.

5.3.2.3 Sediment and Soil

On the basis of a fugacity model, it has been estimated that 2-butoxyethanol partitions into different environmental compartments as follows: 15.98% into air, 0.05% into soil, 83.93% into water, and 0.04% into sediment (ASTER 1995a). 2-Butoxyethanol acetate partitions differently into environmental compartments as follows: 35.1% into air, 0.26% into soil, 64.37% into water, and 0.24% into sediment (ASTER 1995b). Neither compound was predicted to partition into suspended solids or aquatic biota (ASTER 1995a, 1995b). Because of these low partition probabilities into soil and sediment, little research effort has been made to elucidate the fate of either compound in these media. As discussed in Section 5.3.2.2, 2-butoxyethanol does not have any chromophoric group to absorb sunlight incident on the terrestrial surface. Therefore, photolysis of 2-butoxyethanol present in moist soil is not likely. Drawing an analogy from water (see Section 5.3.2.2), it can be concluded that, barring any catalytic effect by component(s) in moist soil or sediment, hydrolysis of 2-butoxyethanol or 2-butoxyethanol acetate is not significant. Aerobic screening studies in water (see Section 5.3.2.2) suggest that aerobic biodegradation is the most important transformation process for both compounds in soil and sediment. The aerobic biodegradation half-life (first order kinetics) of 2-butoxyethanol in soil has been estimated to be 7-28 days (Howard et al. 1991). However, for some soils, as the availability of oxygen decreases with the increase in depth of soil or sediment, the rate of aerobic biotransformation of both compounds decreases. Therefore, both compounds may persist longer in deeper soils and sediments. By direct analogy to estimates of aqueous biodegradation rates (Howard et al. 1991), the rate of anaerobic biodegradation of 2-butoxyethanol in soil may be on the order of 4 times slower than aerobic biodegradation (half-life estimates range from 4 to 16 weeks).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Information on levels of 2-butoxyethanol in air is very limited. 2-Butoxyethanol was reported among 34 major compounds identified in high-volume air samples at a semi-rural site in the United Kingdom;

5. POTENTIAL FOR HUMAN EXPOSURE

however, no concentrations were given (Welch and Watts 1990). Analysis of data from the National Ambient Volatile Organic Compounds (VOCs) Database indicates that, for 14 samples, the daily arithmetic mean and median indoor atmospheric concentrations of 2-butoxyethanol in a non-industrial office setting were 0.214 ppb (v/v) ($1.03 \mu\text{g}/\text{m}^3$) and 0.075 ppb ($0.36 \mu\text{g}/\text{m}^3$), respectively (Shah and Heyderdahl 1988; Shah and Singh 1988). 2-Butoxyethanol was found in only 1 of 6 samples of indoor air from 14 homes in northern Italy, at a concentration of 1.7 ppb ($8 \mu\text{g}/\text{m}^3$) (DeBortoli et al. 1986).

No information was found in the available literature on concentrations of 2-butoxyethanol acetate in air.

5.4.2 Water

Very little information was found in the available literature on concentrations of 2-butoxyethanol in water. 2-Butoxyethanol was detected at a concentration of $23 \mu\text{g}/\text{L}$ in 1 of 7 surface water samples collected in 1979 near The Valley of the Drums, Kentucky, where an estimated 100,000 drums of industrial waste were stored, buried, or dumped between 1967 and 1977 (Stonebreaker and Smith 1980). In Japan, 2-butoxyethanol has been found at concentrations of 1,310 and 5,680 ppb ($\mu\text{g}/\text{L}$) in surface water from the Hayashida River (Uasuhara et al. 1981). The contamination was attributed to effluents from the leather industry. 2-Butoxyethanol has also been found in one groundwater sample from an aquifer beneath a municipal landfill in Norman, Oklahoma (concentration not given) (Dunlap et al. 1976a, 1976b). 2-Butoxyethanol was identified as a contaminant in drinking water in Cincinnati, Ohio; Philadelphia, Pennsylvania; Miami, Florida; New Orleans, Louisiana; Ottumwa, Iowa; and Seattle, Washington. It was also found in finished water from advanced waste treatment plants in Pomona, Escondido, Lake Tahoe, and Orange County, California; Dallas, Texas; and Washington, DC. Concentrations were not reported (Lucas 1984).

Library searching of mass spectral data from water and soil samples from U.S. hazardous waste sites taken between late 1987 and mid-1989 identified 2-butoxyethanol in 110 samples (Eckel et al. 1996). The total number of samples examined was not stated, and the study authors indicate that these data represent minimum occurrences. Although the medium in which the compound was found was not indicated, the properties of 2-butoxyethanol led the study authors to suggest that it was most likely to have been found in water. Among the glycol ethers and related compounds for which the study authors searched, 2-butoxyethanol was found most frequently. Ethylene glycol mono acetate and tripropylene glycol monoethyl ether, were the second and third most frequently identified chemicals.

5. POTENTIAL FOR HUMAN EXPOSURE

No information was found in the available literature on the concentrations of 2-butoxyethanol acetate in surface water, groundwater, or drinking water.

5.4.3 Sediment and Soil

No information was found in the available literature on concentrations of 2-butoxyethanol or 2-butoxyethanol acetate in sediment or soil.

5.4.4 Other Environmental Media

2-Butoxyethanol was found in waste water from a tire plant at an approximate concentration of 0.03 (± 0.009) mg/L (Jungclaus et al. 1976). The detection of 2-butoxyethanol in groundwater underlying a municipal landfill site suggests that this compound may be present in landfill leachates (Dunlap et al. 1976a, 1976b).

In the 1970s, it was estimated that more than 740 products marketed in the United States contained 2-butoxyethanol, at an average concentration of 2.8%; approximately half of these were products for household use (Consumer Products Safety Commission 1977). In a 1978-1982 survey in the Federal Republic of Germany, both 2-butoxyethanol and 2-butoxyethanol acetate were found to occur in 0.4% of 275 different organic solvents commonly used for inks, degreasers, paints, and thinners (concentrations not reported) (Lehmann et al. 1986). A paint stripping formulation was found to contain 35% 2-butoxyethanol (Hahn and Werschulz 1986), whereas the concentration of 2-butoxyethanol in four different paint thinners was found to range from 0% (3 samples) to 5% (w/w) (1 sample) (Yamano et al. 1991). 2-Butoxyethanol has also been found as a volatile organic emission from silicone caulk (Ticbenor and Mason 1988). An epoxy resin contained 7% solvents (2-butoxyethanol, xylene, and methyl-n-amyl ketone) (Rempel et al. 1991). While not detected in a machine cutting fluid prior to use, 2-butoxyethanol was found in the used fluid at a concentration of 0.060 $\mu\text{g/g}$ (60 ppb) (Yasuhara et al. 1986). In a recent survey in France of 1,242 cleaning agent formulations, 10% of the formulations contained 2-butoxyethanol (concentration range, 0.2-80% by volume); approximately 50% of window-cleaning agent formulations tested contained 2-butoxyethanol (concentration range, 1-30% by volume) (Vincent et al. 1993). The concentration of 2-butoxyethanol in aqueous coating systems may vary between 2% and 5%, depending on the formulation (Appelt 1990). The concentration of 2-butoxyethanol acetate used as a retarder solvent in coating formulations is generally 1-5% by volume (Leaf 1985 as cited in NIOSH 1990).

5. POTENTIAL FOR HUMAN EXPOSURE

No information was found in the available literature on concentrations of 2-butoxyethanol or 2-butoxyethanol acetate in food. The estimated BCFs of 2-butoxyethanol and 2-butoxyethanol acetate of only 2 and 9, respectively, in fathead minnows (*Pimephales promelas*) (ASTER 1995a, 1995b), and the evidence against biomagnification of these compounds in the food chain (see Section 5.3.1), indicate that these compounds would not be present in most foods. There is a potential for contamination of food with these compounds, however, from labeling, packaging, and processing activities. Both 2-butoxyethanol and 2-butoxyethanol acetate are indirect food additives that may be used as components of adhesives (FDA 1993a). 2-Butoxyethanol may also be used as a solvent in materials intended for packaging, transporting, holding, or otherwise contacting dry food (FDA 1993b). 2-Butoxyethanol may also be used in washing or to assist in the peeling of fruits and vegetables with lye, and in flume water (at concentrations not to exceed 1 µg /mL) for washing sugar beets (FDA 1993c). There may also be a potential for contamination of plant foods from the minor use of herbicides containing 2-butoxyethanol (Dow 1993; EPA 1993b; Leaf 1985 as cited in NIOSH 1990). A scheme that considered factors such as production volume, pattern of usage, possible fate in the environment, likelihood of the chemical entering the food chain, mechanism of entry into the food chain, persistence and accumulation in the food chain, and toxicity, was used to prioritize chemicals for their potential to contaminate food. A low priority score was obtained for 2-butoxyethanol on the basis of this scheme (Wearne et al. 1996). Among the 70 chemicals ranked, it was ranked lower than 45 chemicals, higher than 8 chemicals, and was given the same ranking as 16 other chemicals.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is exposed to 2-butoxyethanol primarily by inhalation of vapors or dermal absorption during use of common household products that contain this compound as a solvent. At room temperature, 2-butoxyethanol is a liquid with a relatively low vapor pressure (see Table 3-3) and is readily absorbed through the skin (Bartnik et al. 1987; Dugard et al. 1984; Johanson 1988; Johanson and Boman 1991; Johanson et al. 1988, 1989; NIOSH 1990). Therefore, dermal absorption may be the primary route of exposure in cases where protective gloves or other clothing are not worn when using products containing 2-butoxyethanol. It was estimated that approximately half of the more than 740 products containing 2-butoxyethanol that were marketed in the United States in the 1970s were intended for household use. The average concentration of 2-butoxyethanol in these products was 2.8% (Consumer Products Safety Commission 1977). Common household products that contain glycol ethers include acrylic polymers, paints, brake fluids, waxes, cleaning agents, shampoos, degreasing agents, wood finishes, and silicone caulks (Appelt 1990; Browning and Curry 1994; Lewis 1993; NIOSH 1990; Tichenor and Mason 1988; Vincent et al. 1993).

5. POTENTIAL FOR HUMAN EXPOSURE

Similarly, the widespread use of 2-butoxyethanol acetate as a solvent in a wide variety of household products such as inks, stains, paints, lacquers, varnishes, thinners, and degreasers (Lehmann et al. 1986; Lewis 1993; NIOSH 1990) can result in general population exposure through inhalation of vapors and dermal absorption. Non-occupational exposures to 2-butoxyethanol may also occur via ingestion, particularly among populations with contaminated drinking water supplies (Lucas 1984).

No quantitative information was found in the available literature on general population exposures to 2-butoxyethanol or 2-butoxyethanol acetate in the United States.

Occupational exposures to 2-butoxyethanol and 2-butoxyethanol acetate occur via both inhalation of vapors and dermal absorption (Angerer et al. 1990; Johanson et al. 1989; Sohnlein et al. 1993; Vincent et al. 1993, 1996). Because these compounds are liquids at room temperature with relatively low vapor pressures (see Tables 3-3 and 3-4), and are readily absorbed through the skin (Bartnik et al. 1987; Dugard et al. 1984; Johanson 1988; Johanson and Boman 1991; Johanson et al. 1988, 1989; NIOSH 1990), dermal absorption may be predominant or may contribute significantly to overall exposure. Absorption from excessive contact with skin and eyes may occur, particularly when proper protective clothing is not worn.

OSHA requires employers of workers who are occupationally exposed to 2-butoxyethanol to maintain employee exposure at or below the permissible exposure limit (PEL) of 50 ppm (OSHA 1974). The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended a time-weighted average threshold limit value (TWA-TLV) of 25 ppm for occupational exposure to 2-butoxyethanol (ACGIH 1994). The National Institute of Occupational Safety and Health (NIOSH) has set recommended exposure limits (RELs) of 5 ppm for both 2-butoxyethanol and 2-butoxyethanol acetate (NIOSH 1990, 1992). The REL is expressed as a time-weighted average (TWA) exposure for 8 to 10 hours per day over a 40-hour work week. These standards were set taking into account that airborne or direct exposure by the cutaneous route contributes to overall exposure. The NIOSH RELs prohibit direct dermal contact because 2-butoxyethanol and 2-butoxyethanol acetate are readily absorbed through the skin (NIOSH 1990).

Data from the National Occupational Exposure Survey (NOES) conducted by NIOSH from 1980 to 1983 indicate that an estimated 2,139,292 workers in 2,259 industry/occupation categories were potentially exposed to 2-butoxyethanol in the United States from 1981 to 1983, and an estimated 150,892 workers in 236 industry/occupation categories were potentially exposed to 2-butoxyethanol acetate (NIOSH 1989b). These numbers do not include workers potentially exposed to trade-name compounds that contain 2-butoxy-

5. POTENTIAL FOR HUMAN EXPOSURE

ethanol or 2-butoxyethanol acetate. Occupations with the greatest potential for exposure to 2-butoxyethanol included janitors and cleaners; nurses and health aides; hairdressers and cosmetologists; printing, spray painting, metal plating, laundry, dry cleaning, and textile sewing-machine operators; electricians; mining workers; heating, air conditioning, and refrigeration mechanics; electrical power installers and repairers; bus, truck, aircraft, and stationary-engine mechanics; garage and service-station workers; miscellaneous food-preparation workers; plumbers, pipefitters, and steam fitters; automobile mechanics; clinical laboratory technologists and technicians; motor-vehicle assemblers; funeral directors; vehicle washers and equipment cleaners; painters; construction workers; telephone installers and repairers; and furniture and wood-finishers. Occupations with the greatest potential for exposure to 2-butoxyethanol acetate included wood-furniture assemblers and finishers; mining, textile sewing, spray painting, printing, and miscellaneous machine operators; secretaries; janitors and cleaners; automobile-body and related repairers; painters; construction workers; and heavy-equipment, bus, truck, and stationary engine mechanics (NIOSH 1989b).

A survey of chemical exposure in the workplace in Denmark estimated that there were a total of 55,000 exposures to 2-butoxyethanol in 1989 (Brandorff et al. 1995). The industry groups in which exposures occurred were as follows: the manufacture of fabricated metal parts; electrical machinery and apparatus; the manufacture of transport equipment; painters and carpenters; construction, publishing, and printing; wholesale trade; the manufacture of textiles and leather; the manufacture of wood and furniture; the manufacture of chemicals; the manufacture of paints, petroleum, and bitumen products; the manufacture of non-metallic mineral products; the manufacture of precision and optical instruments; the manufacture of plastic; boat building and repair; personal services, cleaning, and hair dressing; sewage and refuse disposal; agriculture, hunting, and forestry; and health services and pharmacies.

There is rather extensive information in the available literature documenting occupational exposures to 2-butoxyethanol. Extremely low exposures have been reported for non-industrial office settings. Data from the National Ambient VOCs database indicate that for 14 samples from non-industrial offices, the daily mean and median indoor atmospheric concentrations of 2-butoxyethanol were 0.24 ppb (v/v) ($1.03 \mu\text{g} / \text{m}^3$) and 0.075 ppb ($0.36 \mu\text{g} / \text{m}^3$), respectively (Shah and Heyderdahl 1988; Shah and Singh 1988). Higher levels of exposure have been found in other occupational settings. Representative information on inhalation exposures of 2-butoxyethanol in various occupations in the United States is summarized in Table 5-1. These data indicate that personal exposures above the NIOSH REL of 5 ppm ($24 \text{ mg} / \text{m}^3$) have been found in silk screening, printing, furniture production, and asbestos/mastic removal, with maximum exposures of 36, 8.3, 9.9, and 22 ppm ($174, 40, 48, \text{ and } 106 \text{ mg} / \text{m}^3$), respectively. It should be noted that the OSHA PEL, the

Table 5-1. Occupational Exposures to 2-Butoxyethanol by Work Site or Process

Work site or process	Number/type of samples	Concentration ^{a,b}		Reference
		Range	Mean	
Silk screening	6/P	1.1–5.3 (5.3–25.5)	3.4 (16.6)	Boiano 1983
Silk screening	3/P	3–5 (14–24)	4 (19)	Apol 1986
Silk screening	NR/P	1.4 (6.8) maximum ^c	NR	Clapp et al. 1984
Silk screening	14/P	13–36 (63–174)	25 (121)	Kullman 1988
	8/A	23–169 (111–817)	63 (304)	
Silk screening				Baker et al. 1985
Silk screeners	16/P	NR	6.8 (32.9)	
Spray painters	5/P	NR	2.6 (12.6)	
Controls	6/P	NR	0.3 (1.4)	
Silk screening/clean-up and maintenance	5/P	1.7–9.8 (8.2–47.4)	5.2 (25.1)	Salisbury et al. 1987
Printing press operation	3/P	<0.04–0.49 (<0.2–2.4)	<0.2 (<1.0)	Lewis and Thoburn 1981
Printing press operation	1/P	8.3 (40.1)	NR	Lee 1988
Printing press operation	2/P	ND ^d –0.53 (ND–2.6)	<0.33 (<1.6)	Kaiser 1990
Label production/plate makers and pressmen	7/P	1–2 (5–10)	2 (10)	Apol 1981
Spray painting	NR/P	0.75 (3.62) ^e	NR	Clapp et al. 1984

Table 5-1 (continued)

Work site or process	Number/type of samples	Concentration ^{a,b}		Reference
		Range	Mean	
Specialty chemical production	NR/P NR/A	ND ^f -0.1 (ND-0.5) ND-1.7 (ND-8.2)	NR, NR	Clapp et al. 1984
Furniture production/finishing	64/P	0.07-9.9 (0.34-48.0)	1.5 (7.1)	Zaebst 1984
Cabinet finishing	6/P	ND ^f -0.4 (ND-1.9)	NR	Newman and Klein 1990
Removal of asbestos-containing mastic	7/P	2-22 (8-107) ^g	12 (60)	Kelly 1993
Hospital housekeeping	4/P	All samples <0.2 (<1.0)	<0.2 (<1.0)	Apol and Cone 1983
Paint formulators	4/P	0.41-3.13	1.26	Foo et al. 1994

^aUnits are ppm, with mg/m³ in parentheses.

^bTime-weighted average

^cMaximum 2-butoxyethanol acetate exposure was 0.75 ppm (4.9 mg/m³).

^dLimit of detection = 0.14 ppm (0.7 mg/m³)

^eReported as "typical" atmospheric concentration

^fLimit of detection not reported

^gSix of seven exposures above the NIOSH REL of 5 ppm

A = area sample; ND = not detected; NIOSH = National Institute for Occupational Safety and Health; NR = not reported; P = personal (breathing zone) sample; REL = Recommend Exposure Limit

5. POTENTIAL FOR HUMAN EXPOSURE

legally enforceable standard for 2-butoxyethanol, is 50 ppm (242 mg/ m³) (OSHA 1974). A maximum exposure to 2-butoxyethanol acetate of 0.75 ppm (4.9 mg/ m³) was reported for workers in a screen printing operation in the United States (Clapp et al. 1984). No other reports of occupational exposure to 2-butoxyethanol acetate in the United States were found in the available literature.

Exposures to 2-butoxyethanol and 2-butoxyethanol acetate were also found in a 1983 survey of 336 Belgian businesses (Veulemans et al. 1987a). In this study, 2-butoxyethanol was found in 25 of 94 air samples from sites using printing pastes; 10 of 81 samples where painting was done; 1 of 20 samples from automobile repair shops; and 17 of 67 samples from various other industrial sites where materials such as varnishes, sterilization agents, and cleaning agents were used. The geometric mean atmospheric concentrations (mg/ m³) and ranges of 2-butoxyethanol at various sites were as follows: printing shops, 4.1 (0.8 ppm), range 1.5-17.7 (0.3-3.7 ppm); painting areas, 18.8 (3.9 ppm), range 3.4-93.6 (0.7-19.4 ppm); automobile repair shops, 5.9 (1.2 ppm) (one sample); various other industries, 8.5 (1.8 ppm), range 0.2-1,775 (<0.1-367 ppm). 2-Butoxy-ethanol acetate was found in 4 of 94 samples from sites using printing pastes, and in 3 of 67 samples from various other industrial sites using materials such as varnishes, sterilization agents, and cleaning agents. The geometric mean atmospheric concentrations (mg/m³) of 2-butoxyethanol acetate were 12.7 (2.6 ppm) at these sites using printing pastes and 10.6 (2.2 ppm) at other industrial sites, respectively; corresponding concentration ranges (mg/ m³) were 4.6-26.5 (1.0-5.5 ppm) and 8.9-11.7 (1.8-2.4 ppm).

Veulemans et al. (1987b) also performed a field study of the urinary excretion of ethoxyacetic acid (EAA) during repeated daily exposure to the ethyl ether of ethylene glycol and the ethyl ether of ethylene glycol acetate. The urinary excretion of EAA was studied in a group of five women daily exposed to the ethyl ether of ethylene glycol and the ethyl ether of ethylene glycol acetate during 5 days of normal production and 7 days after a 12-day production stop. The workers were exposed to a complex solvent mixture containing different ethylene glycol derivatives, esters, alcohols, ketones, and trichloroethane. 2-Butoxyethanol (mean concentration of 3.3 mg/ m³; maximum concentration of 5.7 mg/ m³) was one of the chemicals that the workers were exposed to.

In a survey of occupational exposure to glycol ethers in France that used both atmospheric and biological monitoring, the highest level of exposure to 2-butoxyethanol was among persons cleaning cars (Vincent et al. 1996). The average concentration of 2-butoxyethanol in air was 1.8 ppm, with pre- and post-shift urinary concentrations of 2-butoxyacetic acid of 15.1 and 96.5 mg/g creatinine, respectively. The study authors indicated that exposure of these workers was predominantly by dermal absorption.

5. POTENTIAL FOR HUMAN EXPOSURE

Based on measurements of air concentrations of 2-butoxyethanol in occupational settings and the levels found in consumer products, OECD (1997) has estimated mg/kg/day doses for various occupations and consumer activities. These dose estimates are presented in Table 5-2. Silk screening with a product containing 50% 2-butoxyethanol resulted in the highest dose estimate (18.2 mg/kg/day), followed by cleaning with a product containing 30% 2-butoxyethanol (13.7 mg/kg/day). Painting for 6 hours with a coating containing 1.5% 2-butoxyethanol resulted in an estimated dose of 1.05 mg/kg/day. This report suggested that indirect exposure of the public to 2-butoxyethanol in the environment would be limited to the use of products containing 2-butoxyethanol in public places. Because of the low volatility of 2-butoxyethanol and its high biodegradability, they concluded that exposure in the environment would be minimal.

Because both 2-butoxyethanol and 2-butoxyethanol acetate are readily absorbed through the skin (Bartnik et al. 1987; Dugard et al. 1984; Johanson 1988; Johanson and Boman 1991; Johanson et al. 1988,1989; NIOSH 1990; Truhaut et al. 1979), environmental monitoring of breathing zone or air concentrations in the work area of these substances generally is not adequate to assess overall exposures to these compounds. Biological monitoring of the toxic metabolite, 2-butoxyacetic acid, in urine is considered preferable (Angerer et al. 1990; Johanson 1988; Johanson et al. 1989; Sohnlein et al. 1993; Vincent et al. 1993). Methods are available for the determination of 2-butoxyethanol in blood and urine (Johanson et al. 1986a; Smallwood et al. 1984) (see Chapter 6); however, the utility of 2-butoxyethanol as a biomarker of exposure is limited because of its short half-life (40 minutes) in blood and the small portion of the absorbed dose (<0.03%) excreted unchanged in urine (Johanson et al. 1986a, 1988). In contrast, the half-life of urinary 2-butoxyacetic acid was reported to be 5.77 hours after a controlled, 2-hour inhalation exposure to 2-butoxyethanol, with the amount of 2-butoxyacetic acid excreted in urine corresponding to 15-55% of the absorbed dose of 2-butoxyethanol (Johanson et al. 1986a). 2-Butoxyethanol acetate is rapidly metabolized to 2-butoxyethanol in the body, also resulting in 2-butoxyacetic acid in urine (Johanson 1988; Johanson et al. 1989). Thus, 2-butoxyacetic acid provides a measure of exposure to both 2-butoxyethanol and its acetate. Conjugates of 2-butoxyacetic acid with glutamine in urine have also been measured as a biomarker of exposure to 2-butoxyethanol and 2-butoxyethanol acetate; most exposed people excrete a combination of free and conjugated butoxyacetic acid (Rettenmeier et al. 1993; Sakai et al. 1994). The results of several recent studies evaluating occupational exposures to 2-butoxyethanol and 2-butoxyethanol acetate by environmental and biomonitoring are summarized below.

Twelve workers in a varnish production facility were found to be exposed to 2-butoxyethanol at an average concentration of 1.1 ppm (5.3 mg/m³); individual exposures ranged from <0.1-8.1 ppm (<0.5-39 mg/m³)

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-2. Estimated Occupational and General Exposure to 2-Butoxyethanol^a

Exposure	Maximum vapor concentration	Percentage of exposure period with dermal exposure	Total dose (inhalation and dermal exposure)
Occupational^b			
Manufacture of 2-butoxyethanol	3 ppm (14.5 mg/m ³)	1%	2.2 mg/kg/day
Formulation of products containing 2-butoxyethanol			
10%	2 ppm (9.7 mg/m ³)	20%	1.9 mg/kg/day
30%	10 ppm (145 mg/m ³)	20%	8.2 mg/kg/day
60%	10 ppm (145 mg/m ³)	20%	9.5 mg/kg/day
Cleaning with products containing 2-butoxyethanol			
0.1%	2 ppm (9.7 mg/m ³)	100%	1.4 mg/kg/day
1.0%	2 ppm (9.7 mg/m ³)	100%	1.6 mg/kg/day
10%	4 ppm (19.4 mg/m ³)	100%	5.0 mg/kg/day
30%	10 ppm (145 mg/m ³)	100%	13.7 mg/kg/day
Printing			
Silk screening 50%	10%	100%	18.2 mg/kg/day
General printing 20%	2%	100%	6.0 mg/kg/day
Consumer exposure			
Cleaning ^c	4	100% of 1 hour	0.58 mg/kg/event
Paints/surface coatings 1.5% ^d	2	100% of 6 hours	1.05 mg/kg/day
Cosmetics ^e			
Semi-permanent hair dye	Not applicable	Not applicable	5 mg/day
Permanent hair dye	Not applicable	Not applicable	3.6 mg/day
Environmental exposure	Not estimated	Not estimated	Likely to be minimal

^aDerived from OECD (1997)

^bFor occupational exposure to vapor, a respiratory rate of 1.3 m³/hour and a bioavailability of 0.75 were assumed. For dermal absorption, a skin absorption rate of 0.2 mg/cm²/hour and a skin surface area of 1,000 cm² were assumed. A body weight of 70 kg, and an 8-hour workday were assumed.

^cAssuming a respiratory rate of 0.8 m³/hour and a body weight of 60 kg for a 1 hour cleaning event. For dermal absorption, a skin absorption rate of 0.2 mg/cm²/hour and a skin surface area of 1,000 cm² were assumed.

^dAssuming a respiratory rate of 0.8 m³/hour and a body weight of 60 kg for a 6 hour painting period. For dermal absorption, a skin absorption rate of 0.2 mg/cm²/hour and a skin surface area of 1,000 cm² were assumed.

^eAssuming a concentration of 10% and application of 100 mL once per month for permanent dyes, and 35 mL once per week for semi-permanent dyes. Estimated that 1% of the amount applied may be absorbed.

5. POTENTIAL FOR HUMAN EXPOSURE

(Angerer et al. 1990). Internal exposure was estimated through biological monitoring of 2-butoxyethanol in blood and 2-butoxyacetic acid in urine, where average post-shift (end of work shift) concentrations of these compounds were found to be 121.3 $\mu\text{g}/\text{L}$. and 10.5 mg/L respectively. A markedly lower pre-shift (beginning of work shift) concentration of 2-butoxyacetic acid in the urine (3.3 mg/L) was reported. Most of the exposure was attributed to dermal absorption.

In a study in Germany, 19 workers in the varnish production industry were evaluated for occupational exposures to glycol ethers on the first 2 days of the work week, after an exposure-free weekend (Sohnlein et al. 1993). Urine samples of the workers were collected on the morning of the first day (preshift) and at the end of the second day (postshift). Daily mean concentrations of 2-butoxyethanol from personal air monitoring were 0.5 ppm (2.4 mg/m^3) on the first day and 0.6 ppm (2.9 mg/m^3) on the second day; corresponding daily concentration ranges were <0.1-1.4 ppm (<0.5-6.8 mg/m^3) and <0.1-1.0 ppm (<0.5-4.8 mg/m^3). The mean urinary 2-butoxyacetic acid concentration was 0.2 mg/L on Monday pre-shift and 16.4 mg/L on Tuesday post-shift, with corresponding ranges of <0.02-1.3 mg/L and 0.8-60.6 mg/L . Results of personal air monitoring were too low to account for the post-shift biological monitoring results, indicating the need to conduct biological monitoring to allow more reliable assessment of overall exposure to 2-butoxyethanol.

Similar conclusions were drawn in a recent study conducted in France to evaluate the occupational exposures to 2-butoxyethanol of 16 cleaning women and 13 automobile cleaners using window cleaning agents (Vincent et al. 1993). Concentrations of 2-butoxyethanol in the window cleaning preparations used by these workers ranged from 0.9% to 21.2% by volume. Cleaners of new cars experienced the highest exposures, with time-weighted average concentrations of 2-butoxyethanol from personal samples ranging from <0.10 to 7.33 ppm (<0.5-35.4 mg/m^3). 2-Butoxyacetic acid concentrations in post-shift urinary samples ranged from <12.7 to 371 mg/g creatinine, compared to a range of <2-98.6 mg/g creatinine in pre-shift samples; average 2-butoxyacetic acid concentrations in post- and pre-shift urinary samples ranged from <2 to 178 mg/g creatinine and from <2 to 34.7 mg/g creatinine, respectively. Average urinary 2-butoxyacetic acid concentrations for specific job categories correlated well with work practices (i.e., utilization time and daily quantity of window cleaning agent used). Among workers with the highest exposures, the average 2-butoxyethanol time-weighted average concentration and the average 2-butoxyacetic acid urinary concentration were 2.33 ppm (11.3 mg/m^3) and 111.3 mg/g creatinine, respectively. The authors noted that the high concentrations of urinary 2-butoxyacetic acid, relative to the 2-butoxyethanol time-weighted average concentrations, indicated that dermal absorption was the predominant route of worker exposure. They concluded that for workers in these occupations not wearing protective gloves, environmental sampling

5. POTENTIAL FOR HUMAN EXPOSURE

probably underestimates the 2-butoxyethanol exposure due to dermal absorption, and that biomonitoring of urinary 2-butoxyacetic acid appears to be the best method for estimating overall exposures

Only one study (Johanson et al. 1989) involving biological monitoring of exposures to 2-butoxyethanol acetate was found in the available literature. 2-Butoxyethanol acetate was found in personal air samples from 5 of 19 workers in 4 Swedish silk screen printing facilities at an average time-weighted average concentration of 2.9 mg/ m³ (0.44 ppm) (range, 0.1-10 mg/m³ [0.015-1.5 ppm]). 2-Butoxyacetic acid was found in the urine of 12 of the 19 workers at an average concentration of 8 mol/L (1.2 mg/L) (range, 4-29 mol/L or 0.6-4.2 mg/L).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in occupations involving the production, processing, or use of 2-butoxyethanol or 2-butoxyethanol acetate, or of products containing these substances (see Section 5.5), have the potential to be occupationally exposed to higher concentrations of these substances than the general population. People who live near hazardous waste sites containing 2-butoxyethanol or 2-butoxyethanol acetate and people who live in areas where drinking water is contaminated with 2-butoxyethanol and 2-butoxyethanol acetate may also be subject to exposures; however, no data were found in the available literature to characterize such exposures.

Among the general population, users of household products containing 2-butoxyethanol or 2-butoxyethanol acetate (see Section 5.5) and populations who live in areas where drinking water is contaminated with 2-butoxyethanol or 2-butoxyethanol acetate may be exposed to these chemicals; however, no data were found in the available literature to characterize such exposures. Failure to wear proper protective clothing (e.g., gloves) will increase the potential for high dermal exposures among both the general and worker populations.

5.7 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 2-butoxyethanol and 2-butoxyethanol acetate is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2-butoxyethanol.

5. POTENTIAL FOR HUMAN EXPOSURE

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. Several important physical properties of 2-butoxyethanol and 2-butoxyethanol acetate have yet to be experimentally determined. These include their octanol-water and soil-water partition coefficients, Henry's law constants, and bioconcentration factors in aquatic organisms. These data are important in estimating the fate of the released compounds in the environment and in determining the potential for human exposure. However, reliable estimated values for these parameters are available (ASTER 1995a, 1995b; Howard 1993; HSDB 1995; Lyman et al. 1982) and there is no critical need for experimental confirmation of the estimated values.

Production, Import/Export, Use, Release, and Disposal. Because 2-butoxyethanol and 2-butoxyethanol acetate are contained in a broad array of products that are widely used in the home and in industry (see Sections 4.3 and 5.1), the risk for human exposure may be substantial. The most recent U.S. production data available indicate an increase in production volume of 2-butoxyethanol from approximately 130 million pounds in 1972 to 271 million pounds in 1984 (Gibson 1984 as cited in Ghanayem et al 1987b; HSDB 1995), to more than 300 million pounds in 1986 (NIOSH 1990), and to 408.5 million pounds in 1995 (CMA 1997a). The production volume for 2-butoxyethanol acetate showed a slight decrease from approximately 13.4 million pounds in 1972 to 11 million pounds in both 1975 and 1977 (HSDB 1995; MOSH 1990). More recent production data, as well as data on projections of future production volumes are needed. Similarly, there is a need for recent import/export data for both 2-butoxyethanol and 2-butoxyethanol acetate. The most recent import/export data found for 2-butoxyethanol were from 1984 and indicated an increasing trend in exports from 9 million pounds in 1972 to 71 million pounds in 1984 (Gibson 1984 as cited in Ghanayem et al. 1987b); no import/export data for 2-butoxyethanol acetate were found in the available literature. Information on the uses of 2-butoxyethanol and 2-butoxyethanol acetate is extensive and appears to be adequate. Additional information is needed to characterize releases to the environment of 2-butoxyethanol and 2-butoxyethanol acetate, particularly from facilities that produce or process these chemicals.

5. POTENTIAL FOR HUMAN EXPOSURE

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains information for 1994, became available in May of 1996. This database will be updated yearly and should provide a list of industrial production facilities and emissions. Currently, no information is available in the TRI database for 2-butoxyethanol because the database contains such information only for the general toxic chemical category of glycol ethers and not for specific glycol ethers (EPA 1995). No information is available in the TRI database for 2-butoxyethanol acetate because this chemical is not included under SARA, Title III, and therefore is not among the chemicals that facilities are required to report (EPA 1995). There is a need for such information in order to assess the potential for human exposure to these chemicals from their release from industrial production facilities. Limited or no information was found in the available literature on current disposal methods (including efficiencies, the need for improvement, and the amount disposed of) for 2-butoxyethanol; no information in these areas was found for 2-butoxyethanol acetate. Additional information on disposal methods and the amounts of 2-butoxyethanol and 2-butoxyethanol acetate disposed of by each method is needed.

Environmental Fate. There is a paucity of experimental data regarding the environmental fate of 2-butoxyethanol and 2-butoxyethanol acetate. Fates of these two compounds estimated from their physicochemical properties indicate that a few critical areas need further elucidation. Although it has been estimated that hydrolysis of 2-butoxyethanol acetate is not an important fate process in the environment (ASTER 1995b), experimental confirmation of the rate of hydrolysis under conditions typically found in water and moist soil (pH 5-9) would be helpful. If hydrolysis of 2-butoxyethanol acetate is found to be an important fate determining process, it would be important to identify the products of hydrolysis and assess the health and environmental impacts of the degradation products. Biodegradation studies in natural bodies of water and soil would also be helpful. Both experimental screening studies (Dow 1993; Price et al. 1974; Zahn and Wellens 1980) and estimated half-life values of 7-28 days (Howard et al. 1991) indicate that biodegradation of 2-butoxyethanol and 2-butoxyethanol acetate is one of the important fate determining processes in water and soil. However, biodegradation screening studies conducted with sewage water as inocula may be used to predict the biodegradability under conditions used in water treatment plants. These studies may not be suitable for estimating biodegradability of organic compounds in natural bodies of water and soil. Therefore, it would be helpful to experimentally determine the rates of biodegradation of both of these compounds in soil and natural bodies of water (e.g., by river die-away experiments), and to identify the biodegradation products in these media.

5. POTENTIAL FOR HUMAN EXPOSURE

Bioavailability. 2-Butoxyethanol and 2-butoxyethanol acetate are known to be absorbed following inhalation, ingestion, and dermal contact (Bartnik et al. 1987; Corley et al. 1997; Dugard et al. 1984; Johanson 1988; Johanson and Boman 1991; Johanson et al. 1988,1989; NIOSH 1990; Truhaut et al. 1979). The environmental factors that may influence the bioavailability of 2-butoxyethanol and 2-butoxyethanol acetate from contaminated air, water, soil, or plant material have not been studied. Because these compounds are not strongly sorbed to soil or sediments (see Section 5.3.1), sorption may not be a significant determinant in assessing the bioavailability of 2-butoxyethanol and 2-butoxyethanol acetate from different soils or waters. There is a need for data characterizing the factors that affect the bioavailability of these compounds from environmental media.

Food Chain Bioaccumulation. 2-Butoxyethanol and 2-butoxyethanol acetate do not bioconcentrate significantly in fish (ASTER 1995a, 1995b). The low estimated BCF and K_{ow} values of 2-butoxyethanol and 2-butoxyethanol acetate (see Section 5.3.1 and Tables 3-3 and 3-4), and the ease with which these compounds are metabolized in higher trophic level animals (see Section 2.3) indicate that these compounds will not biomagnify in the food chain. Experimental data on BCFs and food chain bioaccumulation, however, are very limited. Additional data would be desirable.

Exposure Levels in Environmental Media. No data were found in the available literature on concentrations of 2-butoxyethanol and 2-butoxyethanol acetate in ambient outdoor or indoor air. Because of the short half-lives (<1 day; see Section 5.3.2.1) of these chemicals in the atmosphere, neither compound will persist in the atmosphere or be transported long distances. Consequently, significant ambient outdoor concentrations would be expected only in areas near potential emission sources (e.g., production facilities, disposal sites). Data on ambient outdoor and indoor air concentrations of 2-butoxyethanol and 2-butoxyethanol acetate near potential emission sources and at background sites in the United States would be useful. Because of the widespread use of household products containing 2-butoxyethanol and 2-butoxyethanol acetate, additional data on indoor air concentrations of these compounds would be useful to assess indoor exposures of the general population. 2-Butoxyethanol was found in drinking water in a U.S. survey that included Washington, DC, and cities in California, Texas, Ohio, Pennsylvania, Florida, Louisiana, Iowa, and Washington; however, concentrations were not reported (Lucas 1984). Because of the relatively widespread 2-butoxyethanol contamination of U.S. drinking water indicated by this survey, more recent data are needed to assess the potential for exposure of the general public from this source. Data on levels of 2-butoxyethanol acetate in drinking water would also be desirable. 2-Butoxyethanol was detected at a concentration of 23 $\mu\text{g}/\text{L}$ in a surface water sample collected in 1979 at a site in Kentucky where it has been estimated that as many as

5. POTENTIAL FOR HUMAN EXPOSURE

100,000 drums of industrial waste were disposed of between 1967 and 1977 (Stonebreaker and Smith 1980). Examination of mass spectral libraries of data from water and soil samples from U.S. hazardous waste sites taken between late 1987 and mid-1989 identified 2-butoxyethanol in 110 samples (Eckel et al. 1996). The media in which the compound was found was not indicated. No other data were found in the available literature on the levels of 2-butoxyethanol or 2-butoxyethanol acetate in surface or groundwater, or in soil or sediment; such data would be useful to assess the potential for exposure from these media. The low estimated BCF and K_{ow} values of 2-butoxyethanol and 2-butoxyethanol acetate (see Section 5.3.1 and Tables 3-3 and 3-4), and the ease with which these compounds are metabolized in higher trophic level animals (see Section 2.3) indicate that these compounds will not biomagnify in the food chain and, consequently, that concentrations in food will be insignificant; however, there may be some potential for food contamination from packaging and washing procedures (see Section 5.4.4). The minor use of 2-butoxyethanol in herbicides (see Section 4.3) may also present the potential for food contamination by this compound. Data on concentrations of 2-butoxyethanol and 2-butoxyethanol acetate in food would be useful to confirm that consumption of contaminated foods is not a significant route of exposure.

2-Butoxyethanol has been detected in surface water (2 sites), groundwater (7 sites), soil (3 sites) and sediment (1 site) out of 20 of the 1,430 current or former EPA National Priorities List (NPL) hazardous waste sites where it has been detected in some environmental media, whereas 2-butoxyethanol acetate has not been detected at any of the current or former NPL hazardous waste sites (HazDat 1996). The number of sites evaluated for these substances is not known, however. No data were found in the available literature on the concentrations of 2-butoxyethanol and 2-butoxyethanol acetate at NPL sites in any medium.

Reliable monitoring data for the levels of these substances in contaminated media at hazardous waste sites (and background sites) are needed. The information obtained on levels of 2-butoxyethanol and 2-butoxy-ethanol acetate in the environment can be used in combination with the known body burdens of 2-butoxy-ethanol and 2-butoxyethanol acetate to assess the potential risks of adverse health effects in populations living in the vicinity of hazardous waste sites.

No information was found in the available literature on estimates for human intake of 2-butoxyethanol or 2-butoxyethanol acetate from the various environmental media. Such information is necessary to estimate the overall risk of exposure to these substances.

5. POTENTIAL FOR HUMAN EXPOSURE

Exposure Levels in Humans. Because both 2-butoxyethanol and 2-butoxyethanol acetate are readily absorbed through the skin (Bartnik et al. 1987; Dugard et al. 1984; Johanson 1988; Johanson and Boman 1991; Johanson et al. 1988,1989; NJOSH 1990; Truhaut et al. 1979), environmental monitoring of breathing zone or work area air concentrations of these substances generally is not found to be adequate to assess overall exposures to these compounds. Biological monitoring of the toxic metabolite, 2-butoxyacetic acid, in urine is considered preferable (Angerer et al. 1990; Johanson 1988; Sohnlein et al. 1993; Vincent et al. 1993). Limited data on urinary 2-butoxyacetic acid concentrations are available for occupationally exposed groups of the population (see Section 5.5); however, more extensive biomonitoring of workers in a broad range of occupations with potentially high exposures would be useful. Data on urinary 2-butoxyacetic acid concentrations in control groups and in the general population are not available. In addition, biomonitoring data are not available for populations living near hazardous waste sites where 2-butoxyethanol or 2-butoxyethanol acetate are known to be present. These data would be useful in assessing whether this group is being exposed to 2-butoxyethanol or 2-butoxyethanol acetate at levels higher than the general population. This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for 2-butoxyethanol or 2-butoxyethanol acetate were located. These substances are not currently among the compounds for which subregistries have been established in the National Exposure Registry. These substances will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to these substances.

5.7.2 Ongoing Studies

A search of the Federal Research in Progress database (FEDRIP 1995) indicates that no research studies are in progress to fill the data gaps discussed in Section 5.7.1. The Consumer Products Safety Commission is working on a report concerning the uses of ethylene glycol ethers including 2-butoxyethanol.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring 2-butoxyethanol, 2-butoxyethanol acetate, their metabolites, and other biomarkers of exposure and effect to these compounds. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL SAMPLES

Analytical methods for the determination of 2-butoxyethanol, 2-butoxyethanol acetate, and metabolites in biological matrices are shown in Table 6-1. The method of determination in almost all of the methods is gas chromatography (GC) with either electron capture detection (ECD) or flame ionization detection (FID). One of the reported methods used high performance liquid chromatography (HPLC) in conjunction with ultraviolet absorbance detection. 2-Butoxyethanol can be isolated from blood or urine by extraction and analysis (Johanson et al. 1986a; Smallwood et al 1984). The metabolites of 2-butoxyethanol and 2-butoxyethanol acetate include 2-butoxyacetic acid and conjugates of 2-butoxyacetic acid, including the conjugate with glutamine. 2-Butoxyacetic acid and its conjugates are isolated from urine or blood by extraction and are derivatized to increase volatility for GC separation and detection (Begerow et al. 1988; Groeseneken et al. 1989; Johanson 1989; Johanson and Johnsson 1991; Jijnsson and Steen 1978; Sakai et al. 1994) or to enhance detectability for HPLC determinations (Rettenmeier et al. 1993). HPLC has been applied to simultaneously analyze both free 2-butoxyacetic acid and conjugated 2-butoxyacetic acid in the urine (Rettenmeier et al. 1993). Following extraction and derivatization to trimethylsilyl derivatives, free 2-butoxyacetic acid and 2-butoxyacetylglutamine were determined by HPLC. Measurement of both butoxyacetic acid forms allowed for calculation of total butoxyacetic acid. A single gas chromatographic determination of free urinary 2-butoxyacetic acid and total urinary 2-butoxyacetic acid has been described (Sakai et al. 1994). In this procedure, acid hydrolysis of urine is included. Determination of 2-butoxyacetic acid has been used for the

Table 6-1. Analytical Methods for Determining 2-Butoxyethanol, 2-Butoxyethanol Acetate, and Metabolites in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood, urine (BE)	Addition of sodium sulfate and heptanol internal standard to sample followed by extraction with toluene. Addition of pyridine and pentafluorobenzoyl chloride to form derivative of BE. Evaporation of solvent, redissolution in 90% methanol, extraction into hexane, methanol phase discarded, and hexane phase washed with 90% methanol.	GC/ECD	0.1 $\mu\text{mol/L}$ (11.8 $\mu\text{g/L}$; 11.8 ppb, w/v)	No data (method reproducibility of 11% RSD)	Johanson et al. 1986a
Urine (BAA)	Addition of 200 μL urine to glass vial containing pentoxyacetic acid (internal standard), 2 mL tetrabutylammonium hydrogen sulfate buffered to pH 6 with potassium phosphate, 2 mL dichloromethane, and 10 μL pentafluorobenzyl bromide. Rotation for 20 hours at room temperature followed by isolation and evaporation of dichloromethane phase, redissolution in hexane and dilution.	GC/ECD	4 $\mu\text{mol/L}$ (528 $\mu\text{g/L}$; 528 ppb, w/v)	No data (method %RSD = 2)	Johanson 1989
Blood (BAA)	Addition of 200 μL whole blood to glass vial containing pentoxyacetic acid as internal standard, tetrabutylammonium as counter ion, dichloromethane, and pentafluorobenzyl bromide. Rotation for 20 hours at room temperature followed by isolation and evaporation of dichloromethane phase, redissolution in hexane.	GC/ECD	0.04 $\mu\text{mol/L}$ (5.33 $\mu\text{g/L}$; 5.33 ppb, w/v)	No data (method %RSD = 7.5)	Johanson and Johnson 1991
Urine (BAA)	Addition of NaCl and HCl to 2 mL of urine followed by 3 extractions with ethyl acetate and solvent exchange to toluene. Formation of trimethylsilyl ethers.	GC/MS	No data	No data	Jönsson and Steen 1978

Table 6-1 (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine (BAA)	Adjustment of urine to pH 7; addition of 3-chloropropionic acid (internal standard) and lyophilization overnight. Dissolution of residue in methanol containing pentafluorobenzyl bromide followed by equilibration at 90 °C for 3 hours. Addition of water and extraction of esters with dichloromethane.	GC/FID	0.03 mg/L (0.03 ppm, w/v)	95.1% (average of 3.5 %RSD)	Groeseneken et al. 1989
Blood (BE)	Extraction of whole blood with dichloromethane followed by filtration of organic layer and volume reduction.	GC/FID	4.0 µg/g (4 ppm, w/w)	81% (range 64–105%; 20% RSD)	Smallwood et al. 1984
Urine (BAA)	Addition of external standard to 50 mL urine, adjustment of pH to 1–2 and removal of cationic impurities by cation-exchange. Isolation of BAA by adsorption onto XAD-4 resin and elution using diethyl ether. Evaporation of solvent followed by derivatization with diazomethane.	GC/FID	0.02 mg/L (0.02 ppm, w/v)	100.9% (%RSD ranged from 4.8 to 12.6)	Begerow et al. 1988
Urine (BAA)	Addition of saturated aqueous sodium chloride, acidification with HCl, extraction three times with ethyl acetate. Evaporation of solvent, redissolution in toluene followed by removal of water. Addition of methoxylamine-hydrochloride followed by N,O-bis-(trimethylsilyl)-trifluoroacetamide.	GC/MS	No data	No data	Jönsson and Steen 1978
Blood (BE)	Addition of sodium heparin and an ion-pairing reagent (sodium hydroxide and tetrabutylammonium hydrogen sulfate). Addition of pentafluorobenzyl chloride followed by heating.	GC/MS	16–18 ng/g	Range from 92.3–103.4%	Bormett et al. 1995

Table 6-1 (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood (BAA)	Addition of sodium heparin and an ion-pairing reagent (sodium hydroxide and tetrabutylammonium hydrogen sulfate). Extractive alkylation performed by adding pentafluorobenzyl bromide and methylene chloride. Mixture was vortex-mixed and separated by centrifuge. The methylene chloride layer was analyzed by GC.	GC/MS	16–18 ng/g	Range from 102.1–107.8%	Bormett et al. 1995
Urine (BAA, N-butoxyacetyl-glutamine)	Adjustment of pH of urine sample to pH 2–3 after addition of pentoxoacetic acid and 2-ethylhexyloxyacetic acid-glutamine conjugate as internal standards. Extraction with ethyl acetate, isolation of organic layer and solvent evaporation. Derivatization with 4-nitrobenzylbromide at 80 °C for 30 minutes.	HPLC/UV	BAA: <0.08 $\mu\text{mol/mL}$ (10.6 ppm, w/v); BAA-glutamine: <0.09 $\mu\text{mol/mL}$ (24.9 ppm, w/v)	No data	Rettenmeier et al. 1993
Urine (total BAA, free plus conjugated)	Addition of internal standard, acidification and boiling for 1 hour. Extraction with dichloromethane: isopropanol (2:1, v/v) and formation of trimethylsilyl esters.	GC/FID	0.05 mg/L (0.05 ppm, w/v)	100.8% (3.3% RSD)	Sakai et al. 1994

BAA = 2-butoxyacetic acid; BE = 2-butoxyethanol; BEA = 2-butoxyethanol acetate; ECD = electron capture detector; FID = flame ionization detection; GC = gas chromatography; HCl = hydrochloric acid; HPLC = high performance liquid chromatography; MS = mass spectrometry; NaCl = Sodium chloride; RSD = relative standard deviation; UV = ultraviolet absorbance detection; v/v = volume/volume; w/v = weight/volume

6. ANALYTICAL METHODS

biological monitoring of 2-butoxyethanol exposure (refer to sections 2.3 “Toxicokinetics” and 2.6 “Biomarkers of Exposure and Effect”). It is noteworthy, however, that biological monitoring studies typically measure only free 2-butoxyacetic acid. Since a substantial fraction of 2-butoxyacetic acid is eliminated as the amino acid conjugate, exposure levels to 2-butoxyethanol would be underestimated in these typical biological monitoring studies.

6.2 ENVIRONMENTAL SAMPLES

Routine analyses for the glycol ethers in water, including 2-butoxyethanol and its acetate are often not completed because frequently used general-purpose GC/MS methods designed to measure priority pollutants do not readily detect these compounds (Eckel et al. 1996). For example, recovery of 2-butoxyethanol was 6.7% by EPA method 625 for semivolatiles.

Analytical methods specific for the determination of 2-butoxyethanol and 2-butoxyethanol acetate in environmental matrices are shown in Table 6-2. The method of determination in all of the methods is GC in conjunction with either flame ionization detection (FID) or mass spectrometric (MS) detection. Sample preparation methods for air samples are based on the adsorption of the target compounds onto a sorbent such as charcoal (Guest et al. 1985; NIOSH 1994a; OSHA 1990) or Amberlite XAD-7 (Andersson et al. 1982) followed by elution of the compounds with a solvent. Carbon disulfide has been used to recover non-polar analytes from charcoal but fails to recover the more polar 2-butoxyethanol and 2-butoxyethanol acetate (Fracchia et al. 1977; Mueller and Miller 1979). As a result, solvents such as 5% methanol in dichloromethane are used and provide good recoveries of both target compounds (NIOSH 1994a; OSHA 1990). Although thermal desorption is frequently used to recover volatile analytes from sorbents, this technique often fails with charcoal because the temperature required for volatilization of strongly adsorbed compounds results in the decomposition of the analytes, especially in the presence of water (Cocheo et al. 1987). Adsorbed samples generally appear to be stable but NIOSH (1994a) recommends freezer storage of samples until elution to minimize any decomposition. High concentrations of less volatile analytes and water can impact the retention of 2-butoxyethanol and 2-butoxyethanol acetate on charcoal, so the analyst must be aware that premature breakthrough could result under these conditions and when large air volumes are sampled (NIOSH 1994a; Posner and Okenfuss 1981). The analytic methods for determining 2-butoxyethanol in air samples allow for the detection of 2-butoxyethanol at concentrations that include the inhalation MRLs.

Table 6-2. Analytical Methods for Determining 2-Butoxyethanol and 2-Butoxyethanol Acetate in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (validated for BE; should be applicable to BEA)	Sorption of analytes onto charcoal followed by elution with 5% (v/v) methanol in dichloromethane.	GC/FID (NIOSH Method 1403, Issue 2)	1 mg/m ³ (0.21 ppm, v/v) with 10 L air sample	92% (6.5% RSD)	NIOSH 1994
Air (BE, BEA)	Sorption of analytes onto charcoal followed by elution with 5% (v/v) methanol in dichloromethane.	GC/FID (OSHA Method 83)	BE: 150 µg/m ³ (31 ppb, w/v) with 48 L sample; BEA: 116 µg/m ³ (24 ppb, w/v) with 48 L sample	BE: 99% (5.2% RSD); BEA: 101.5% (5.5% RSD).	OSHA 1990
Air (BE)	Sorption of analytes onto XAD-7 sorbent followed by elution with diethyl ether.	GC/FID	<50 mg/m ³ (10.5 ppm, v/v, with 5 L sample)	95% (4% RSD) at 50.8 mg/m ³ (10.5 ppm, v/v)	Andersson et al. 1982
Groundwater (BE)	Addition of deuterated internal standard and direct injection.	GC/MS	0.4 mg/L (0.4 ppm, w/v)	88.2% at 5 mg/L	Beihoffer and Ferguson 1994
River water (BE)	Vacuum distillation followed by continuous liquid-liquid extraction (24-hour) with ether and concentration of dried extract using Kuderna-Danish device.	GC/MS	No data	No data	Yasuhara et al. 1981
Waste water (BE)	Purge and trap of VOCs from water containing sodium sulfate onto Tenax-GC. Water removal using dry purge followed by thermal desorption.	GC/MS	No data	No data	Michael et al. 1991
Waste water (BE)	Extraction of acidified water with dichloromethane for 6 hours followed by drying and concentration of extract.	GC/MS	No data	No data	Jungclaus et al. 1976

BE = 2-butoxyethanol; BEA = 2-butoxyethanol acetate; GC = gas chromatography; MS = mass spectrometry; NIOSH = National Institute for Occupational Safety and Health; RSD = relative standard deviation; v/v = volume/volume; w/v = weight/volume

6. ANALYTICAL METHODS

Preparation methods for water samples are based on purge and trap (Michael et al. 1991), solvent extractions (Jungclaus et al. 1976; Nguyen et al. 1994; Yasuhara et al. 1981), or direct injection (Beihoffer and Ferguson 1994). High concentrations of dissolved solids in sample extracts can contaminate the GC injector or column after only a few analyses (Beihoffer and Ferguson 1994), so adequate quality control procedures should be in place. Yasuhara et al. (1981) included a vacuum distillation step of highly polluted river water prior to solvent extraction to avoid the contamination of the extract with high molecular weight, non-volatile compounds. The method of determination steps of all of the methods found for water were based on GC/FID or GC/MS.

6.3 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 2-butoxyethanol or 2-butoxyethanol acetate is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 2-butoxyethanol and 2-butoxyethanol acetate.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods are available for the determination of 2-butoxyethanol in blood and urine (Johanson et al. 1986a; Smallwood et al. 1984). The utility of 2-butoxyethanol as a biomarker of exposure is limited because of its short elimination half-time in blood (40 minutes) and the small fraction of the absorbed dose (less than 0.03%) excreted unchanged in urine (Johanson 1988; Johanson et al. 1986a). In contrast, the half-time of urinary 2-butoxyacetic acid was reported to be 5.77 hours after a controlled, 2-hour exposure to 2-butoxyethanol (Johanson et al. 1986a). The amount of 2-butoxyacetic acid excreted in urine corresponded to 17-55% of the absorbed dose of 2-butoxyethanol and will thus serve as a sensitive marker of exposure (Johanson et al. 1986a). Sensitive and reproducible methods

6. ANALYTICAL METHODS

for 2-butoxyacetic acid are available. No methods were found for the determination of 2-butoxyethanol acetate in physiological matrices, but this ester is rapidly metabolized to 2-butoxyethanol in the body resulting in 2-butoxyacetic acid in urine (Johanson 1988; Johanson et al. 1989). Thus, 2-butoxyacetic acid will provide measures of exposure to both 2-butoxyethanol and its acetate. Conjugates of 2-butoxyacetic acid with glutamine have been measured in urine and methods exist to determine the 2-butoxyacetic acid glutamine conjugate (Rettenmeier et al. 1993) or 2-butoxyacetic acid after hydrolysis of the conjugate (Sakai et al. 1994). The method of Sakai et al. (1994) permits the calculation of 2-butoxyacetic acid conjugate concentrations based on determinations of 2-butoxyacetic acid with and without hydrolysis; this method provides measurements of total (2-butoxyacetic acid and 2-butoxyacetic acid conjugates) and free 2-butoxyacetic acid, respectively. No new methods are needed.

Methods for Determining Parent Compounds and Degradation Products in Environmental

Media. Methods exist for the determination of 2-butoxyethanol in air (Andersson et al. 1982; NJOSH 1994a; OSHA 1990), groundwater (Beihoffer and Ferguson 1994), river water (Yasuhara et al. 1981), and waste water (Jungclaus et al. 1976; Michael et al. 1991; Nguyen et al. 1994). Methods also exist for the determination of 2-butoxyethanol acetate in air (NJOSH 1994a; OSHA 1990). Limits of detection (LOD) for these compounds in air are in the sub-ppm range. Only one reported method for 2-butoxyethanol in water appeared to be characterized, and an LOD of less than 0.4 ppm (1.9 mg/m^3) was claimed (Beihoffer and Ferguson 1994). Additional information is needed about the method LODs for 2-butoxyethanol in water and waste water; additional methods are needed for other matrices (i.e., wastes, soils). No method was found for 2-butoxyethanol acetate in a matrix other than air; additional methods for other matrices are needed. No studies were found in which the concentrations of these two compounds were determined in foods. Methods are needed if contamination of foodstuffs and the resultant human exposure via ingestion is of concern.

6.3.2 Ongoing Studies

No ongoing method development studies were found.

7. REGULATIONS AND ADVISORIES

The national regulations and guidelines regarding 2-butoxyethanol and 2-butoxyethanol acetate in air, water, and other media are summarized in Table 7-1.

An MRL of 6 ppm has been derived for acute-duration inhalation exposure (14 days or less) to 2-butoxyethanol, based on a NOAEL of 50 ppm for hematotoxicity in pregnant rats (Tyl et al. 1984). An MRL of 3 ppm has been derived for intermediate-duration inhalation exposure to 2-butoxyethanol, based on a NOAEL of 25 ppm for hematotoxicity in rats (Dodd et al. 1983). An MRL of 0.2 ppm has been derived for chronic inhalation exposure (365 days or longer) to 2-butoxyethanol, based on a NOAEL in humans for statistically significant decreased hematocrit and increased mean corpuscular hemoglobin concentrations (Haufrond et al. 1992). The observed changes were still within the range of normal human variability.

An MRL of 0.4 mg/kg/day has been derived for acute-duration oral exposure to 2-butoxyethanol, based on a LOAEL of 32 mg/kg for hematotoxicity in 16-month old rats (Ghanayem et al. 1987a). An MRL of 0.07 mg/kg/day has been derived for intermediate-duration oral exposure to 2-butoxyethanol, based on a LOAEL of 69 mg/kg/day for mild hepatic toxicity in rats (NTP 1993).

There is no reference dose (RfD) for 2-butoxyethanol or 2-butoxyethanol acetate. A risk assessment to establish a reference concentration (RfC) for 2-butoxyethanol is under review by an EPA Workgroup (IRIS 1995).

OSHA requires employers of workers who are occupationally exposed to 2-butoxyethanol to institute engineering controls and work practices to reduce employee exposure and maintain it at or below permissible exposure limits (PEL). The PEL for 2-butoxyethanol is 50 ppm (OSHA 1974). Workers exposed to 2-butoxyethanol should wear personal protective equipment such as gloves, coveralls, and goggles to protect exposure to the skin (OSHA 1974). NIOSH recommends that industrial hygiene surveys be completed at work places where airborne exposure to 2-butoxyethanol or 2-butoxyethanol acetate may occur (NIOSH 1990). If exposure levels are at or above one-half the recommended exposure limit (REL = 5 ppm), NIOSH recommends that a program of personal monitoring be instituted so that the exposure of each worker can be estimated. If exposure levels are at or greater than the REL, or if there is a potential for skin contact, NIOSH recommends that 2-butoxyacetic acid be measured in the urine of the workers.

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to 2-Butoxyethanol and 2-Butoxyethanol Acetate

Agency	Description	Information	References
<u>INTERNATIONAL</u>			
Guidelines:			
WHO	No information available		WHO 1984
<u>NATIONAL</u>			
Regulations:			
a. Air:			
EPA OAQPS	List of Chemicals Produced By Affected Facilities (2-butoxyethanol acetate)	Yes	40 CFR 60.489 EPA 1977
	List of Chemicals Produced By Affected Facilities (2-butoxyethanol)	Yes	40 CFR 60.489 EPA 1977
	Chemicals Affected By Standards of Performance for Volatile Organic Emissions from Synthetic Organic Chemical Manufacturing Industry Distillation Operations (2-butoxyethanol)	Yes	40 CFR 60.667 EPA 1990b
	Chemicals Affected by Standards of Performance for Volatile Organic Compound Emissions from Synthetic Organic Chemical Manufacturing Industry Reactor Processes (2-butoxyethanol)	Yes	40 CFR 60.707 EPA 1993a
	Synthetic Organic Chemical Manufacturing Industry Chemicals (2-butoxyethanol)	Yes	40 CFR 63.106 EPA 1992
	Synthetic Organic Chemical Manufacturing Industry Chemicals (2-butoxyethanol acetate)	Yes	40 CFR 63.106 EPA 1992
	Organic HAPs Subject to the Wastewater Provisions for Process Units at New and Existing Sources and Corresponding Fraction Removed (Fr) Values (2-butoxyethanol acetate)	Yes	40 CFR 63 Subpart G EPA 1994
OSHA	Permissible Exposure Limit (TWA) ^a (2-butoxyethanol)	50 ppm (240 mg/m ³) skin ^b	29 CFR 1910.100 OSHA 1974
b. Water:			
EPA OW	Effluent Guidelines and Standards - Organic Chemicals, Plastics, and Synthetic Fibers - Bulk Organic Chemicals (2-butoxyethanol)	Yes	40 CFR 414 Subpart G EPA 1987
c. Other:			
EPA OPPTS	Tolerance Range for Agriculture Products (2-butoxyethanol)	Conditionally Exempted From Tolerance	40 CFR 180.1001 EPA 1971
	Preliminary Assessment Information Manufacturer Report (2-butoxyethanol)	Yes	40 CFR 712.30 EPA 1982
	Substance Subject to All Provisions of Health and Safety Data Reporting (2-butoxyethanol)	Yes	40 CFR 716.120 EPA 1986

7. REGULATIONS AND ADVISORIES

Table 7-1 (continued)

Agency	Description	Information	References
<u>NATIONAL</u> (cont.)			
DOT	Hazardous Materials and Special Provisions - Table 1 (2-butoxyethanol)	Yes	49 CFR 172.101 DOT 1990
Guidelines:			
a. Air:			
ACGIH	TLV-TWA for Occupational Exposure (2-butoxyethanol) ^e	25 ppm (121 mg/m ³) skin ^b	ACGIH 1997
NIOSH	Recommended Exposure Limit for Occupational Exposure (TWA) (2-butoxyethanol) ^d	5 ppm (24 mg/m ³) skin ^b	NIOSH 1994
	Recommended Exposure Limit for Occupational Exposure (TWA) (2-butoxyethanol acetate) ^d	5 ppm (33 mg/m ³) skin ^b	NIOSH 1994
b. Other:			
ACGIH	Under Study to Establish or Change Biological Exposure Indices (2-butoxyethanol)	Yes	ACGIH 1997
<u>STATE</u>			
Regulations and Guidelines:			
a. Air: Average Acceptable Ambient Air Concentrations (2-butoxyethanol)			
AZ	24 hours	9 mg/m ³	NATICH 1992
CT	8 hours	2.4 mg/m ³	
FL (Pinellas Co.)	8 hours	1.2 mg/m ³	
	24 hours	0.3 mg/m ³	
ND	8 hours	1.21 mg/m ³	
OK	24 hours	2.42 mg/m ³	
SD	8 hours	24 mg/m ³	
TX	30 minutes	1.21 mg/m ³	
	Annual	0.121 mg/m ³	
VA	24 hours	2 mg/m ³	
VT	8 hours	12 mg/m ³	
WA-SWEST	24 hours	0.4 mg/m ³	

7. REGULATIONS AND ADVISORIES

Table 7-1 (continued)

Agency	Description	Information	References
<u>STATE</u> (Cont.)			
	Average Acceptable Ambient Air Concentrations (2-butoxyethanol acetate)		NATICH 1992
AZ	1 hour 24 hours	720 $\mu\text{g}/\text{m}^3$ 190 $\mu\text{g}/\text{m}^3$	
TX	30 minutes Annual	1.35 mg/m^3 135 $\mu\text{g}/\text{m}^3$	

^aTime-Weighted average concentrations that must not be exceeded during any 8-hour work shift of a 40-hour work week.

^bSkin designation that there is a potential for dermal absorption and that skin exposure should be prevented through the use of gloves, coveralls, goggles, and other appropriate equipment.

^cACGIH TLV-TWA is the time-weighted average concentration for an 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed, day after day, without adverse effects.

^dRecommended exposure limit is a time-weighted average concentration for up to a 10-hour workday during a 40-hour workweek.

ACGIH = American Conference of Governmental Industrial Hygienists; DOT = Department of Transportation; EPA = Environmental Protection Agency; HAPs = Hazardous Air Pollutants; NATICH = National Air Toxics Information Clearinghouse; NIOSH = National Institute for Occupational Safety and Health; OAQPS = Office of Air Quality Planning and Standards; OPPTS = Office of Pollution Prevention and Toxic Substances; OSHA = Occupational Safety and Health Administration; OW = Office of Water; TLV = Threshold Limit Value; TWA = Time Weighted Average; WHO = World Health Organization

7. REGULATIONS AND ADVISORIES

2-Butoxyethanol is regulated under the Clean Water Act's Effluent Guidelines as stated in Title 40, Part 414 of the *Code of Federal Regulations*. The point source category for which 2-butoxyethanol is controlled as a bulk organic chemical is organic chemicals, plastics, and synthetic fibers (EPA 1987).

Both 2-butoxyethanol and 2-butoxyethanol acetate are regulated under the Clean Air Act, including National Emission Standards for Hazardous Air Pollutants (NESHAPs).

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9. GLOSSARY

Acute Exposure-Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc})-The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d)-The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF)-The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL)-The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen-A chemical capable of inducing cancer.

Ceiling Value-A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure-Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity-The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity-Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory-An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)-The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure-Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

9. GLOSSARY

Immunologic Toxicity-The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals

In Vitro-Isolated from the living organism and artificially maintained, as in a test tube.

In vivo-Occurring within the living organism.

Lethal Concentration₍₁₀₎ (LC_{LO})-The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀)-A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose₍₁₀₎ (LD_{LO})-The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀)-The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀)-A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)-The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations-Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level-An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen-A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity-The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL)-The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})-The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL)-An allowable exposure level in workplace air averaged over an 8-hour shift.

9. GLOSSARY

q1*-The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu\text{g}/\text{L}$ for water, $\text{mg}/\text{kg}/\text{day}$ for food, and $\mu\text{g}/\text{m}^3$ for air).

Reference Dose (RfD)-An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)-The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity-The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL)-The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity-This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen-A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)-A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a <1.

Time-Weighted Average (TWA)-An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD₅₀)-A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF)-A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the US Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

APPENDIX A

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL, may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

Chemical name(s): 2-Butoxyethanol
 CAS number(s): 111-76-2
 Date: June 1998
 Profile status: Draft 3
 Route: [X] Inhalation [] Oral
 Duration: [X] Acute [] Intermediate [] Chronic
 Key to figure: 21
 Species: Rat

MRL: 6 [] mg/kg/day [X] ppm [] mg/m³

Reference: Tyl et al. 1984

Experimental design: Timed-pregnant Fischer 344 rats (n=36) were exposed to 2-butoxyethanol vapors by inhalation on Gd 6–15 at concentrations 0, 25, 50, 100, or 200 ppm for 6 hours per day (Tyl et al. 1984). The animals were observed for clinical signs throughout the study, and food and water consumption (withheld during exposures) were measured. Maternal body weights were taken on Gd 0, 6, 9, 12, 15, and 21. The animals were sacrificed on Gd 21 after obtaining blood samples. Hematology and organ weights (uterus, liver, thymus, spleen, and kidney) were evaluated. Hematologic determinations on dams showed significant reductions in erythrocyte (RBC) count, mean corpuscular hemoglobin concentration (MCHC), and an increase in hemoglobin per cell (MCH) and size of the red blood cell (MCV) at 100 and 200 ppm exposure, but not at 50 ppm. There were significant increases in hemoglobin and hematocrit counts at 200 ppm. Clinical signs that occurred with an incidence different from the controls were observed in 75% of dams in the 200 ppm group during the exposure period, and included the clear evidence of hematuria or hemoglobinuria, periocular wetness, perinasal encrustation, pale and cold extremities, and necrosis of the tail tip. Periocular wetness, clear evidence of hematuria, and perinasal discharge were also noted in 25–50% of the dams in the 100 ppm dose group. In the 25 and 50 ppm dose groups, 25% of the dams showed signs of periocular wetness. Maternal body weight gain was decreased 29% in the 100 ppm group at Gd 6–15, compared to the control group. Exposure to 200 ppm resulted in negative weight gain and decreased (at Gd 6–21) maternal body weight (11–12% at 200 ppm), decrease in food consumption at Gd 6–15 during treatment (13% decrease at 100 ppm), and evidence of anemia. Decreased water consumption (14%) was noted at 200 ppm. There was a reduction in maternal gravid uterine weight at 200 ppm. Relative kidney weight was elevated as compared to controls at 200 ppm in the presence of decreased body weight. No treatment-related effects were observed on the weights of the liver.

Effects noted in study and corresponding doses: A clear dose response relationship was observed for hematological and renal toxicity:

50 ppm = low dose (NOAEL)

100 ppm = mid dose (Serious LOAEL: females showed decreased erythrocyte (RBC) count, mean corpuscular hemoglobin concentration (MCHC), an increase in hemoglobin per cell (MCH) and size of the red blood cell (MCV); clear evidence of hematuria noted in 25–50% of the dams)

200 ppm = high dose (decreased erythrocyte (RBC) count, mean corpuscular hemoglobin concentration (MCHC), an increase in hemoglobin per cell (MCH) and size of the red blood cell (MCV); significant increases in hemoglobin and hematocrit counts; clear evidence of hematuria or hemoglobinuria in 75% of the dams)

APPENDIX A

Dose endpoint used for MRL derivation: 50 ppm - hematological effects

NOAEL LOAEL

Uncertainty factors used in MRL derivation: 9

1 3 10 (for use of a LOAEL)

1 3 10 (for extrapolation from animals to humans)

1 3 10 (for human variability)

An uncertainty factor of 3 for animal to human extrapolation because *in vitro* data show that human red blood cells are much less sensitive to the hemolytic effects of the 2-BUTOXYETHANOL metabolite, 2-butoxyacetic acid.

Concentrations of 2-butoxyacetic acid that caused hemolysis of rat red blood cells did not cause hemolysis of human red blood cells (Bartnik et al. 1987). For example, following a 60 minute exposure of rat red blood cells to 7.5 mM 2-butoxyacetic acid 100% hemolysis was observed. Following a 60 minute exposure of human red blood cells to 15 mM 2-butoxyacetic acid, no hemolysis was observed (Bartnik et al. 1987). An *in vitro* study measuring more sensitive endpoints of red blood cell effects, mean cell volume and hematocrit, has also shown rat red blood cells to be more sensitive to 2-butoxyacetic acid compared to human red blood cells (Ghanayem and Sullivan 1993). For example, following a 1 hour exposure to 2 mM 2-butoxyacetic acid, mean corpuscular volume was about 150% of controls in rat red blood cells, and 105% of controls in human red blood cells, hematocrit was about 155% of controls in rat red blood cells, and 105% of controls in human red blood cells. Red blood cells of rabbits, hamsters, mice and baboons were also sensitive to the red blood cell effects of 2-butoxyacetic acid, while red blood cells of cats, pigs, dogs, and guinea pigs were not sensitive to the effects of 2-butoxyacetic acid (Ghanayem and Sullivan 1993). This *in vitro* data is also supported by the Carpenter et al. (1956) study in which erythrocyte osmotic fragility, an effect observed in animals, was not observed in humans exposed by inhalation to ≤ 195 ppm 2-butoxyethanol for 4-8 hours. In addition, an *in vitro* study showed that human erythrocytes were resistant to the hemolytic effects of 2-butoxyacetic acid, the hemolytic metabolite of 2-butoxyethanol (Udden 1994).

An uncertainty factor of 3 for human variability was used because the results of *in vitro* data suggest that 2-butoxyethanol does not cause significant hemolysis of normal and potentially susceptible erythrocytes (Udden 1996). Udden (1994) reported that red blood cells in humans (including the elderly and patients with hereditary spherocytosis and sickle cell disease) were not susceptible to 2-butoxyacetic acid-induced hemolysis.

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

If so, explain: Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The human equivalent dose (HEC) was calculated using Formula 4-48 from Interim Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, EPA (1994). Though 2-butoxyethanol is a Category 2 gas (i.e., water soluble and accumulates in blood), the equation in the EPA (1994) document for extrarrespiratory effects of Category 2 gases is presently under review and the recommended equation is that for Category 3 gases:

$$\text{NOAEL}_{[\text{HEC}]} = \text{NOAEL}_{[\text{ADJ}]} \times (\text{H}_{\text{b/g}})_{\text{A}} / (\text{H}_{\text{b/g}})_{\text{H}}$$

where:

$\text{NOAEL}_{[\text{HEC}]}$ = the NOAEL human equivalent concentration

APPENDIX A

NOAEL _[ADJ]	=	the NOAEL adjusted for duration (see below)
(H _{b/g}) _A	=	blood/gas partition coefficient for animals
(H _{b/g}) _H	=	blood/gas partition coefficient for humans
(H _{b/g}) _A	=	not available
(H _{b/g}) _H	=	7965 (Johanson and Dynesius 1988).

Because a blood/gas partition coefficient was not available for rats, a default of 1 was used for the ratio of partition coefficients.

Thus,

$$\text{NOAEL}_{[\text{HEC}]} = 50 \text{ ppm} \times (1)$$

$$\text{NOAEL}_{[\text{HEC}]} = 50 \text{ ppm}$$

Was a conversion used from intermittent to continuous exposure? If so, explain: No adjustment for intermittent exposure was used because 2-butoxyethanol and its major metabolite, 2-butoxyacetic acid, are eliminated from the body within 24 hours. In addition, because of the high blood/gas partition coefficient (7965) relative to a low fat/blood partition coefficient (0.77 Jepson et al. 1992) blood concentrations would be expected to reach periodicity (i.e., the periodic steady state is such that the concentration versus time profile is the same for every week) during acute duration exposure (EPA 1994).

Other additional studies or pertinent information that lend support to this MRL: Although in the Tyl et al. (1984) study, periocular wetness was observed at high incidences in the rats at ≥ 25 ppm, indicating that 25 ppm is a minimal LOAEL for eye irritation (from direct contact of the eyes with the vapor during inhalation exposure), hemolysis is the most consistently observed critical effect of concern for exposure to 2-butoxyethanol. Furthermore, the use of 25 ppm as a minimal LOAEL for eye irritation would result in an acute MRL lower than the intermediate inhalation MRL (see Work Sheet below).

That hemotoxicity is a critical end point of concern is supported by other acute inhalation studies. In Dodd et al. (1983), Fischer 344 rats (8 male, 8 female) were exposed for 9 days, 6 hours per day, 5 days per week to 2-butoxyethanol target concentrations of 0, 25, 100, or 250 ppm (mean average concentrations determined by gas chromatography to be 0, 20, 86, or 245 ppm, respectively). Rats were observed for signs of toxicity during exposure and 14 days postexposure. Necropsies were performed on animals that died and on survivors killed at the end of the observation period. Biological assessments included daily animal observations, body weight and organ (kidney, liver, lungs, and testes) weight determinations and ophthalmologic, hematologic, and gross pathologic examinations. The mean chamber concentrations of 25, 100, and 250 ppm 2-butoxyethanol (BE) were determined by gas chromatography to be 20, 86, and 245 ppm, respectively. A few male rats exposed to 245 ppm were observed to have audible respiration and nasal discharge. There was no effect on the hematologic parameters in rats exposed to 20 ppm BE (NOAEL). At 86 ppm exposure (LOAEL), in both sexes there was a significant, but less profound, effect on the erythroid parameters. At 245 ppm exposure, both male and female rats showed significantly depressed red blood cells (RBC) of 21% below control values, hemoglobin (HGB) and mean corpuscular concentration (MCHC) and significant increases in mean corpuscular volume (MCV), nucleated RBC, and reticulocytes. Red-stained urine was also

APPENDIX A

observed in rats of both sexes exposed to 245 ppm, but this staining was never observed again. Female rats exposed to 86 ppm showed significantly higher liver weights. Male and female rats of the 245 ppm group also showed increased liver weights. Decreased mean body weight gains (% not provided) were also found. A 14-day postexposure recovery showed substantial reversal of the affected blood parameters. In another study, nonpregnant rats were exposed to 250 ppm or greater 2-butoxyethanol by inhalation for 6.5 hours (Nelson et al. 1984). The exposed rats exhibited hematuria 4-6 hours after onset of exposure at all concentrations (LOAEL = 250 ppm). Surviving rats in each dose group had necrotic tail tips 1 week after exposure. New Zealand White rabbits (n=24) were exposed to 2-butoxyethanol vapors by inhalation on Gd 6-1 8 at concentrations 0,25,50, 100, or 200 ppm for 6 hours per day (Tyl et al. 1984). The animals were observed for clinical signs throughout the study. Food and water were withheld during exposures. Maternal body weights were taken on Gd 0,6,9, 12, 15, 18,21, and 29. The animals were sacrificed on Gd 29 after obtaining blood samples. Hematology and organ weights (uterus, liver, thymus, spleen, and kidney) were evaluated. Hematologic determinations in rabbits indicated no apparent treatment-related changes in any parameter evaluated. Statistically significant increases in hemoglobin content (13.5 g/dL versus 12.4 g/dL in controls) and hematocrit were seen at 100 ppm but not at 200 ppm, suggesting to the authors a biphasic response of the hematological system to 2-butoxyethanol exposure in rabbits. Therefore, 100 ppm appears to be a LOAEL and 50 ppm appears to be the NOAEL for hematological effects in the rabbits, but the authors did not present a mechanism to explain the apparent biphasic response that these effects were not seen at 200 ppm.

The data indicating that humans are less susceptible to 2-butoxyethanol-induced hemolysis are as follows: In *in vitro* experiments designed to examine the effect of 2-butoxyethanol on human and rat erythrocytes (Bartnik et al. 1987), and *in vitro* experiments designed to examine the effect of 2-butoxyacetic acid on the erythrocytes of various mammalian species (including human species) indicated species-dependent sensitivity to the hemolytic effects of 2-butoxyethanol and 2-butoxyacetic acid. In this regard, rodents, rabbits, and baboons were more sensitive than pigs, dogs, cats, guinea pigs, and humans.

In its Threshold Limit Value (TLV) recommendation, the American Conference of Governmental Industrial Hygienists (ACGIH) stated that "anemia is not an uncommon condition in the human population. (ACGIH 199 1). ACGIH (199 1) recommended that exposures to 2-butoxyethanol be maintained below levels that are found to cause blood changes in experimental animals. Based on this recommendation, the TLV-TWA was established at 25 ppm.

Agency Contact (Chemical Manager): Olivia Harris

APPENDIX A

Chemical name(s): 2-Butoxyethanol
 CAS Number(s): 111-76-2
 Date: June 1998
 Profile status: Draft 3
 Route: Inhalation Oral
 Duration: Acute Intermediate Chronic
 Key to figure: 42
 Species: Rat

MRL: 3 mg/kg/day ppm mg/m³

Reference: Dodd et al. 1983

Experimental design: Fischer 344 rats (16 male, 16 female) were exposed for 90 days, 6 hours per day, 5 days per week to 2-butoxyethanol target concentrations of 0,5,25, or 75 ppm (mean average concentrations determined by gas chromatography to be 0,5,25, or 77 ppm, respectively). Rats were observed for signs of toxicity during exposure and 14 days postexposure. Necropsies were performed on animals that died and on survivors killed at the end of the observation period. For hematology evaluation only, 6 rats/sex/group were killed after 6 weeks. Biological assessments included daily animal observations, body weight and organ (kidney, liver, lungs and testes) weight determinations, and ophthalmologic, hematologic, and gross pathologic examinations. In addition, RBC osmotic fragility tests, serum chemistries, urinalysis, and histologic examination of selected tissues of the high BE concentrations were assessed. No deaths occurred throughout the study. There were no clinical signs of toxicity observed. There was a transient decrease in body weight gain (exposure weeks 24; data not shown) of females exposed to 77 ppm 2-butoxyethanol. After 6 weeks (3 1 exposures), female rats exposed to 77 ppm had slight but significant decreases (13% below control values) in red blood cell counts (RBC) and hemoglobin (HGB) accompanied with an 11% increase above control value in mean corpuscular hemoglobin (MCH). At the end of the 90-day study, the hematologic effects seen in the female exposed rats either lessened or returned to control value ranges. The only significant hematologic finding in male rats was a 5% decrease in RBC at 77 ppm after 66 exposures. The red blood cell osmotic fragility tests of both 2-butoxyethanol-treated rats and controls were similar. No treatment-related differences were found in body weight, organ weights, urine or serum chemistries, gross lesions, or microscopic lesions in males or females.

Effects noted in study and corresponding doses:

25 ppm = mid dose (NOAEL)

77 ppm= high dose (Serious LOAEL: female rats had 13% decrease in red blood cells (RBC) and 4% decrease in hemoglobin [HGB] accompanied with an 11% increase above control value in mean corpuscular hemoglobin [MCH]; male rats had a 5% decrease in RBC)

Dose endpoint used for MRL derivation: 25 ppm - hematological effects

NOAEL LOAEL

Uncertainty factors used in MRL derivation: 9

1 3 10 (for use of a LOAEL)

APPENDIX A

[] 1 [X] 3 [] 10 (for extrapolation from animals to humans)

[] 1 [X] 3 [] 10 (for human variability)

An uncertainty factor of 3 for animal to human extrapolation was used because *in vitro* data show that human red blood cells are much less sensitive to the hemolytic effects of the 2-butoxyethanol metabolite, 2-butoxy-acetic acid. Concentrations of 2-butoxyacetic acid that caused hemolysis of rat red blood cells did not cause hemolysis of human red blood cells (Bartnik et al. 1987). For example, following a 60 minute exposure of rat red blood cells to 7.5 mM 2-butoxyacetic acid 100% hemolysis was observed. Following a 60 minute exposure of human red blood cells to 15 mM 2-butoxyacetic acid, no hemolysis was observed (Bartnik et al. 1987). An *in vitro* study measuring more sensitive endpoints of red blood cell effects, mean cell volume and hematocrit, has also shown rat red blood cells to be more sensitive to 2-butoxyacetic acid compared to human red blood cells (Ghanayem and Sullivan 1993). For example, following a 1 hour exposure to 2 mM 2-butoxyacetic acid, mean corpuscular volume was about 150% of controls in rat red blood cells, and 105% of controls in human red blood cells, hematocrit was about 155% of controls in rat red blood cells, and 105% of controls in human red blood cells. Red blood cells of rabbits, hamsters, mice and baboons were also sensitive to the red blood cell effects of 2-butoxyacetic acid, while red blood cells of cats, pigs, dogs, and guinea pigs were not sensitive the effects of 2-butoxyacetic acid (Ghanayem and Sullivan 1993). This *in vitro* data is also supported by the Carpenter et al. (1956) study in which erythrocyte osmotic fragility, an effect observed in animals, was not observed in humans exposed by inhalation to ≤ 195 ppm 2-butoxyethanol for 4-8 hours. In addition, an *in vitro* study showed that human erythrocytes were resistant to the hemolytic effects of 2-butoxyacetic acid, the hemolytic metabolite of 2-butoxyethanol (Udden 1994).

An uncertainty factor of 3 for human variability was used because the results of *in vitro* data suggest that 2-butoxyethanol does not cause significant hemolysis of normal and potentially susceptible erythrocytes (Udden 1996). Udden (1994) reported that red blood cells in humans (including the elderly and patients with hereditary spherocytosis and sickle cell disease) were not susceptible to 2-butoxyacetic acid-induced hemolysis.

Was a conversion factor used from uum in food or water to a mg/body weight dose?

If so, explain: Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

The human equivalent dose (HEC) was calculated using Formula 4-48 from Interim Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, EPA (1994). Though 2-butoxyethanol is a Category 2 gas (i.e., water soluble and accumulates in blood), the equation in the EPA (1994) document for extrarrespiratory effects of Category 2 gases is presently under review and the recommended equation is that for Category 3 gases:

$$\text{NOAEL}_{[\text{HEC}]} = \text{NOAEL}_{[\text{ADJ}]} \times (\text{H}_{\text{b/g}})_{\text{A}} / (\text{H}_{\text{b/g}})_{\text{H}}$$

where:

$\text{NOAEL}_{[\text{HEC}]}$	=	the NOAEL human equivalent concentration
$\text{NOAEL}_{[\text{ADJ}]}$	=	the NOAEL adjusted for duration (see below)
$(\text{H}_{\text{b/g}})_{\text{A}}$	=	blood/gas partition coefficient for animals
$(\text{H}_{\text{b/g}})_{\text{H}}$	=	blood/gas partition coefficient for humans

APPENDIX A

$(H_{b/g})_A$ = not available
 $(H_{b/g})_H$ = 7965 (Johanson and Dynesius 1988).

Because a blood/gas partition coefficient was not available for rats, a default of 1 was used for the ratio of partition coefficients.

$$\text{NOAEL}_{[\text{HEC}]} = 25 \text{ ppm} \times (1)$$

$$\text{NOAEL}_{[\text{HEC}]} = 25 \text{ ppm}$$

Was a conversion used from intermittent to continuous exposure? If so, explain: No adjustment for intermittent exposure was used because 2-butoxyethanol and its major metabolite, 2-butoxyacetic acid, are eliminated from the body within 24 hours. In addition, because of the high blood/gas partition coefficient (7965) relative to a low fat/blood partition coefficient (0.77 Jepson et al. 1992) blood concentrations would be expected to reach periodicity (i.e., the periodic steady state is such that the concentration versus time profile is the same for every week) during intermediate-duration exposure (EPA 1994).

Other additional studies or pertinent information that lend support to this MRL: In addition to the hematologic effects, a transient decrease in body weight was observed in females early in the study. In light of the results of Dodd et al. (1983) after acute inhalation exposure of rats to doses up to 245 ppm, and the more severe hematological effects observed, accompanied by changes in liver weight, respiratory effects, and decreased body weight gain, it seems reasonable to accept the effect seen in the intermediate inhalation exposure experiment as being the most sensitive indicator of toxicity. No other suitable supporting studies were found.

In its Threshold Limit Value (TLV) recommendation, the American Conference of Governmental Industrial Hygienists (ACGIH) stated that "anemia is not an uncommon condition in the human population. (ACGIH 1991). ACGIH (1991) recommended that exposures to 2-butoxyethanol be maintained below levels that are found to cause blood changes in experimental animals. Based on this recommendation, the TLV-TWA was established at 25 ppm.

Agency Contact (Chemical Manager): Olivia Harris

APPENDIX A

Chemical Name: 2-Butoxyethanol
CAS Number: 111-76-2
Date: June 1998
Profile Status: Draft 3
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 51
Species: Human

MRL: 0.2 mg/kg/day ppm

Reference: Haufroid et al. 1997

Experimental design:

Thirty-one male workers exposed to 2-butoxyethanol were studied. Twenty workers were exposed to an average concentration of 0.75 ppm, and 11 workers were exposed to an average concentration of 0.46 ppm. The weighted average of the means for the two groups of workers is 0.6 ppm. The workers were exposed for 1 to 6 years. The workers were also exposed to methyl ethyl ketone. Exposure concentrations of methyl ethyl ketone were not provided. Studies in animals indicate that methyl ethyl ketone does not produce hematologic effects (ATSDR 1992). The average urinary concentrations of methyl ethyl ketone were 0.27 mg/g creatinine. Twenty-one unexposed men that worked for the same company served as controls; however, 2-butoxyethanol concentrations in the air the controls breathed were not assayed. Urine was collected before the shift and at the end of the shift and assayed for free 2-butoxyacetic acid (thought to be the toxic metabolite), retinol binding protein, and creatinine. Rettenmeier et al. (1993) and Sakai et al. (1994) found that some of the 2-butoxyacetic acid (BAA) in the urine of humans is excreted as amino acid conjugates. Rettenmeier et al. (1993) reported that the ratio of the amino acid conjugate of butoxyacetic acid to total butoxyacetic acid ranged from 0.16 to 0.64 (mean value 0.48). Thus, free BAA in urine does not represent all internal dosing. Blood was collected and assayed for red blood cell counts, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, haptoglobin, reticulocytes, and osmotic resistance. Serum alanine aminotransferase and aspartate aminotransferase were also measured. The exposed workers wore gloves, thus minimizing dermal exposure. In addition, two exposure groups were combined together for the analysis of measured parameters.

Effects noted in study and corresponding doses:

Urinary concentrations of free 2-butoxyacetic acid ranged from not detected to 1.1 mg/g creatinine before shift (average 0.3), and 0.3 to 51.4 mg/g creatinine after shift (average 12.2) in persons exposed to an average of 0.76 ppm. Urinary concentrations of free 2-butoxyacetic acid ranged from not detected to 3.4 mg/g creatinine before shift (average 0.6), and 0.6 to 20.4 mg/g creatinine after shift (average 9.2) in persons exposed to an average of 0.46 ppm. A significant correlation ($r = 0.55$, $p = 0.0012$) was observed between endshift urinary free 2-butoxyacetic acid concentrations and 2-butoxyethanol in air. There was no effect on red blood cell numeration, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, haptoglobin, reticulocyte numeration, osmotic resistance, hepatic (aspartate aminotransferase, alanine aminotransferase) and renal (plasmatic creatinine, urinary retinol binding protein) parameters. Two small but statistically significant differences in hematology values were observed: a significant decrease ($p=0.03$) in hematocrit values (exposed: $43.9\% \pm 2.1$, range: 39.9-50.7, controls: $45.5\% \pm 2.7$, range: 40.6-50.4) and a significant ($p=0.02$) increase in mean corpuscular hemoglobin concentration (exposed: $33.6 \text{ g/dL} \pm 0.9$, range: 31.8-35.6; controls: $32.9 \text{ g/dL} \pm 1.1$, range: 31.1-35.6). ATSDR considers these differences to be consistent with hemolysis observed in animal studies, and they may be early indicators of potential adverse effects in humans. However,

APPENDIX A

because the changes in both hematocrit and mean corpuscular hemoglobin concentration were in the range of normal clinical values, the effect was considered a NOAEL. Normal clinical values of hematocrit are reported for males as 40-54%, with a level of 30% or less considered to indicate moderate to severe anemia (Fischbach 1992). Normal clinical values of mean corpuscular hemoglobin concentration are reported as 31-37 g hemoglobin/dL (Fischbach 1992). Increased mean corpuscular hemoglobin concentrations often indicates spherocytosis, while decreased mean corpuscular hemoglobin concentrations may indicate macrocytic anemia, chronic blood loss anemia, or pyridoxine-responsive anemia (Fischbach 1992). None of the red blood cell end points were correlated with internal exposure as assessed by urinary free 2-butoxyacetic acid. [Although as noted above a significant fraction of BAA in urine may have been conjugated.] Serum creatinine and urinary retinol binding protein were not affected. No difference was observed for serum alanine transaminase or serum aspartate transaminase. The statistics in this paper seem odd.

Dose and end point used for MRL derivation:

NOAEL LOAEL

0.6 ppm

Uncertainty Factors used in MRL derivation: 3

1 3 10 (for use of a LOAEL)
 1 3 10 (for extrapolation from animals to humans)
 1 3 10 for human variability

An uncertainty factor of 3 for human variability was used because the results of *in vitro* data suggest that 2-butoxyethanol does not cause significant hemolysis of normal and potentially susceptible erythrocytes (Udden 1996). Udden (1994) reported that red blood cells in humans (including the elderly and patients with hereditary spherocytosis and sickle cell disease) were not susceptible to 2-butoxyacetic acid-induced hemolysis. At the end of a 90-day inhalation study, the hematologic effects seen in the female exposed rats either lessened or returned to control value ranges (Dodd et al 1983).

Was a conversion used from ppm in food or water to a mg/body weight dose?

If so, explain: Not applicable

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: Not applicable

Other additional studies or pertinent information which lend support to this MRL:

There are no additional chronic studies in either humans or animals.

Agency Contact (Chemical Manager): Olivia Harris

APPENDIX A

Chemical name(s): 2-Butoxyethanol
 CAS Number(s): 111-76-2
 Date: June 1998
 Profile status: Draft 3
 Route: Inhalation Oral
 Duration: Acute Intermediate Chronic
 Key to figure: 28
 Species: Rat

MRL: 0.4 mg/kg/day ppm mg/m³

Reference: Ghanayem et al. 1987a

Experimental design: Young (4-5 weeks) and adult (9-13 weeks, 5-6 months, and 16 months) rats were dosed with 0,32,63, 125,250, or 500 mg/kg 2-butoxyethanol by gavage. Hemotoxicity and metabolism and excretion of 2-butoxyethanol was monitored for 48 hours. Animals were killed at 24 and 48 hours after treatment and spleen, liver, kidney, testes, and urinary bladder were weighed, fixed, and examined. Histopathological results were presented for the control, 125,250, and 500 mg/kg dose group.

Effects noted in study and corresponding doses: In younger rats, 125 mg/kg caused no effect on hematological parameters. At 500 mg/kg, RBC, HGB, and HCT were decreased, although not as much as in the older rats. In older rats, 2-butoxyethanol at 125 mg/kg causes severe acute hemolytic anemia resulting in significant decreases at 8 and 24 hours after treatment in RBCs, HGB, and HCT, and increases 8 hours after administration in the concentration of free plasma hemoglobin. At 4 hours, peak increases in free plasma hemoglobin were seen in both younger and older rats dosed with 500 mg/kg. Secondary to the hemolytic effects, 2-butoxyethanol also caused hemoglobinuria in 16-month-old rats at ≥ 32 mg/kg, in 6-month-old rats at ≥ 63 mg/kg, and in younger rats (4-13 weeks) at ≥ 125 mg/kg. Other effects secondary to hemolysis consisted of histopathologic changes in the liver and kidney, including focal coagulative necrosis of hepatocytes at 250 mg/kg (1/6) and hemoglobin casts in the proximal tubules of the kidney at 125 mg/kg in adult (9-13 weeks) rats; these effects were not seen in young (4-5 weeks) rats even at 500 mg/kg. These effects of 2-butoxyethanol were dose- and time-dependent, and were more severe at 24 hours after treatment than at 48 hours after treatment. The onset of the development of hemoglobinuria followed the decline in the concentration of free HGB in the plasma. Both the hemolytic effects and the secondary effects of 2-butoxyethanol were age-dependent, with older rats being more sensitive than younger rats. The 4-5-week-old rats and 9-13-week-old rats were treated with 500 mg/kg/day 2-butoxyethanol, and reticulocytes and leukocytes were counted up to 48 hours after treatment. Adult rats exhibited neutrophilic leukocytosis and mild lymphopenia within 4 hours. This was not detected at 48 hours. An absolute increase in reticulocyte count occurred at 48 hours after dosing. Thus,

32 mg/kg = LOAEL.

Dose endpoint used for MRL derivation: 32 mg/kg - hematological effects

NOAEL LOA L

Uncertainty factors used in MRL derivation: 90

1 3 10 (for use of a LOAEL)
 1 3 10 (for extrapolation from animals to humans)
 1 3 10 (for human variability)

APPENDIX A

Since the 32 mg/kg dose in the Ghanayem et al. (1987a) study caused hemoglobinuria only in the aged rats, the uncertainty factor used for human variability was 3 since the LOAEL is for the most sensitive population. Also, *in vitro* data show that human red blood cells are much less sensitive to the hemolytic effects of the 2-butoxyethanol metabolite, 2-butoxyacetic acid. Concentrations of 2-butoxyacetic acid that caused hemolysis of rat red blood cells did not cause hemolysis of human red blood cells (Bartnik et al. 1987). For example, following a 60 minute exposure of rat red blood cells to 7.5 mM 2-butoxyacetic acid 100% hemolysis was observed. Following a 60 minute exposure of human red blood cells to 15 mM 2-butoxyacetic acid, no hemolysis was observed (Bartnik et al. 1987). An *in vitro* study measuring more sensitive endpoints of red blood cell effects, mean cell volume and hematocrit, has also shown rat red blood cells to be more sensitive to 2-butoxyacetic acid compared to human red blood cells (Ghanayem and Sullivan 1993). For example, following a 1 hour exposure to 2 mM 2-butoxyacetic acid, mean corpuscular volume was about 150% of controls in rat red blood cells, and 105% of controls in human red blood cells, hematocrit was about 155% of controls in rat red blood cells, and 105% of controls in human red blood cells. Red blood cells of rabbits, hamsters, mice and baboons were also sensitive to the red blood cell effects of 2-butoxyacetic acid, while red blood cells of cats, pigs, dogs, and guinea pigs were not sensitive the effects of 2-butoxyacetic acid (Ghanayem and Sullivan 1993). This *in vitro* data is also supported by the Carpenter et al. (1956) study in which erythrocyte osmotic fragility, an effect observed in animals, was not observed in humans exposed by inhalation to ≤ 195 ppm 2-butoxyethanol for 4-8 hours.

An uncertainty factor of 3 was used for human variability because the LOAEL is from a sensitive subpopulation (older animals). Also, an uncertainty factor of 3 for human variability was used because the results of *in vitro* data suggest that 2-butoxyethanol does not cause significant hemolysis of normal and potentially susceptible erythrocytes (Udden 1996). Udden (1994) reported that red blood cells in humans (including the elderly and patients with hereditary spherocytosis and sickle cell disease) were not susceptible to 2-butoxyacetic acid-induced hemolysis.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? If so, explain:
Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure?
If so, explain: Not applicable

Other additional studies or pertinent information that lend support to this MRL: Since the severity of hemoglobinuria in the 16-month-old rats increased as the dose levels increased and since hemoglobinuria occurred in younger rats only at higher doses (Ghanayem et al. 1987a), the 32 mg/kg dose was considered to be a less serious LOAEL. The use of the 32 mg/kg as a Less serious LOAEL for the derivation of the acute oral MRL is supported by a study in pregnant rats, in which no hematological effects were found at a similar dose of 30 mg/kg/day given for 3 days during gestation (NTP 1989) (see discussion below). Since the 32 mg/kg dose in the Ghanayem et al. (1987a) study caused hemoglobinuria only in the aged rats, the uncertainty factor used for human variability was 3, since the LOAEL is for the most sensitive population. Furthermore, since humans appear to be less susceptible to 2-butoxyethanol-induced hemolysis (see below), the uncertainty factor used for extrapolation from animals to humans was 3.

Hemolytic anemia is the characteristic toxic reaction to 2-butoxyethanol in animals. Sperm-positive Fischer 344 rats (27-33 per dose group) were administered 0,30, 100, and 200 mg/kg/day 2-butoxyethanol (BE) in distilled water by gavage for Gd 9-11 (NTP 1989). The biological effects of BE on dams were assessed during treatment as well as 24 hours after treatment and on Gd 20, and on fetuses at sacrifice

APPENDIX A

(Gd 20); 22-24 females per group were confirmed pregnant. At sacrifice on Gd 12 or 20, each pregnant female was examined by counting number of corpora lutea, and weighing body, liver, right and left kidney, spleen and uterus. For females sacrificed on Gd 20, the uterine contents were also evaluated (i.e., number of implantation sites, resorptions, and dead and live fetuses). The fetuses were sexed and examined for external and visceral malformations. Maternal and fetal blood (pooled by litter) was analyzed for red (RBC) and white (WBC) blood cell counts, hemoglobin (HGB), hematocrit (HCT), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and platelet count. RBC count and corresponding measures of HCT and HGB were significantly reduced in the 100 and 200 mg/kg/day dose groups at approximately 24 hours after the final dose. MCHC was significantly decreased at the high dose group. The blood dyscrasia produced at approximately 24 hours after the last treatment also included increases in reticulocytes (%RBC), WBC count, platelet count, MCV, and MCH in the 100 and 200 mg/kg/day dose groups. On Gd 20, maternal hematological end points recovered toward control values, although a majority of values remained different from controls on the 100 and 200 mg/kg/day dose groups. RBC counts measured on Gd 20 in the 100 and 200 mg/kg/day dose groups of each treatment period were still significantly lower than control values, but counts had increased since cessation of treatment (i.e., at 200 mg/kg/day dose group), the RBC count increased to 91% of control levels by Gd 20. Similarly, reticulocytes declined from values measured earlier in the 100 and 200 mg/kg/day dose groups, but were still significantly above the control level. Corrected WBC count measured on Gd 20 after dam treatment was similar across dose groups. Platelet counts determined at the end of the study after treatment showed a significant decreasing trend with dose which appeared to be determined by a nonsignificant decreasing trend with the high-dose group below the control count. The MCV and MCH on Gd 20 exhibited significant dose-related trends with the values of the two highest dose groups significantly greater than the control values. Calculated values of MCHC showed significant decreasing dose-related trends with the high-dose group values lower than controls. The changes in MCHC with treatment, although significant at the high-dose group, were relatively slight. The maternal hematological profiles at 24 hours after final treatment and at Gd 20 indicate that 2-butoxyethanol-induced hemolysis triggered a compensatory hematopoietic response leading to reticulocytosis. Furthermore, recovery was more complete by Gd 20 for dams treated on Gd 9-11 than those exposed to Gd 1-13.

In a similar experiment by NTP (1989), sperm-positive female Fischer 344 rats (29-31 per dose group) were administered 0, 30, 100, and 300 mg/kg/day 2-butoxyethanol in distilled water by gavage for Gd 1-13. The biological effects of BE on dams were assessed during treatment as well as 24 hours after treatment and on Gd 20, and on fetuses at sacrifice (Gd 20). Maternal and fetal blood (pooled by litter) was analyzed for red (RBC) and white (WBC) blood cell counts, hemoglobin (HGB), hematocrit (HCT), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and platelet count. RBC count and corresponding measures of HCT and HGB were significantly reduced in the 100 and 300 mg/kg/day dose groups at approximately 24 hours after the final dose. MCHC was significantly decreased at the high dose group. The blood dyscrasia produced at approximately 24 hours after the last treatment also included increases in reticulocytes (%RBC), WBC count, platelet count, MCV, and MCH in the 100 and 300 mg/kg/day dose groups. On Gd 20, maternal hematological end points recovered toward control values, although a majority of values remained different from controls on the 100 and 300 mg/kg/day dose groups. RBC counts measured on Gd 20 in the 100 and 300 mg/kg/day dose groups of each treatment period were still lower than control values, but counts had increased since cessation of treatment (i.e., at 300 mg/kg/day dose group), the RBC count increased from about 45% of control levels at 24 hours after the final treatment to 80% of control levels by Gd 20. Similarly, reticulocytes declined from values measured earlier in the 100 and 300 mg/kg/day dose groups, but were still significantly above the control level. Corrected WBC count measured on Gd 20 after dam treatment still exhibited a significant increasing trend with dose which appeared to be determined by a nonsignificant increase in the high-dose group. Platelet counts determined at the end of the study after treatment showed a significant increase at the high dose. The MCV and MCH on Gd 20 exhibited significant dose-related trends with the values of the two highest dose

APPENDIX A

groups greater than the control values. Calculated values of MCHC showed significant decreasing dose-related trends with the high-dose group values lower than controls. The changes in MCHC with treatment, although significant at the high-dose group, were relatively slight. The maternal hematological profiles at 24 hours after final treatment and at Gd 20 indicate that BE-induced hemolysis triggered a compensatory hematopoietic response leading to reticulocytosis. Furthermore, recovery was more complete by Gd 20 for dams treated on Gd 9-11 than those exposed to Gd 11-13. Thus, 30 mg/kg/day was the NOAEL for hematological effects in both experiments in the NTP (1989) study, lending support for the use of the LOAEL of 32 mg/kg for hematological effects in the aged rats in the Ghanayem et al. (1987a) study for the derivation of the acute oral MRL.

In another study (Ghanayem et al. 1992) male Fischer 344 rats (n=6) received by gavage 125 mg/kg/day 2-butoxyethanol for 1, 2, 3, 6, or 12 consecutive days. Controls received 5 mL water/kg body weight daily for 12 consecutive days. Twenty-four hours after the last dose, blood samples were collected for hematological measurements and determination of blood ATP concentration. Spleen and liver were removed and weighed. Organ weight per 100 g body weight ratios were calculated. Treatment of rats with 2-butoxyethanol daily (125 mg/kg/day) for 1-3 consecutive days resulted in a time-dependent increase in the hemolysis of erythrocytes. However, when daily treatment with 2-butoxyethanol continued beyond 3 days, the number of erythrocytes began to rebound and approached pretreatment levels within 12 days despite continued daily exposure, suggesting development of tolerance to the hemolytic effect of 2-butoxyethanol. Mean cell volumes (MCV), ATP concentration, and the number of reticulocytes increased to the sixth day and then decreased on the twelfth day. Liver weight/body weight ratios were minimally affected by repeated dosing, declined on days 3 and 6, but increased on day 12 as compared to controls. Spleen weight increased in a time-dependent manner.

In other studies, hematotoxic effects were observed at similar or higher doses. For instance, hemoglobinuria was observed in rats receiving one dose of 126 mg/kg (Corley et al. 1994); hemolysis was observed in rats receiving one dose of 250 mg/kg, and reduced BBC, hematocrit, and increased MCV and reticulocytes, and mean corpuscular hemoglobin in the presence of increased liver and spleen weight were observed in rats at 500 mg/kg/day after 1 or 4 days (Ghanayem and Sullivan 1993; Ghanayem et al. 1987b; Grant et al. 1985). Hepatic and renal histopathology similar to that observed in Ghanayem et al. (1987a) at 125 mg/kg/day was also observed at 500 mg/kg/day after one dose (Ghanayem et al. 1987b).

Agency Contact (Chemical Manager): Olivia Harris

APPENDIX A

Chemical name(s) : 2-Butoxyethanol
CAS Number(s): 111-76-2
Date: June 1998
Profile status: Draft 3
Route: [] Inhalation [X] Oral
Duration: [] Acute [X] Intermediate [] Chronic
Key to figure: 90
Species: Rat

MRL: 0.07 [X] mg/kg/day [] ppm [] mg/m³

Reference: NTP 1993

Experimental design: F344/N rats (10 males, 10 females) were given targeted concentrations of 0,750, 1,500,3,000,4500, or 6,000 ppm 2-butoxyethanol in drinking water daily for 13 weeks. Actual doses, determined by the authors from drinking water consumption and body weight data, were: 0,69, 129,281, 367, and 452 mg/kg/day for males and 0, 82, 151, 304, 363, and 470 mg/kg/day for females. Animals were observed twice daily and weighed at the start of the studies, weekly thereafter, and at necropsy. Clinical observations were recorded weekly. Water consumption by cage was measured twice a week. Complete necropsies were performed on all animals in the base studies. The heart, liver, right kidney, lung, thymus, and right testis were weighed, examined for gross lesions, fixed or embedded in paraffin, and stained for microscopic examination. The protocol for the 13-week studies required that tissues be examined microscopically in all control animals, animals in the highest dose group with at least 60% survivors, and all animals in the higher-dose group (inclusive of early deaths and survivors). In the clinical pathology study, 20 males and 20 females per dose group were used. On days 5 and 21, blood samples were collected for the clinical pathology and hematology studies. Week- 13 analyses were conducted on samples obtained from rats in the base studies. Urinalysis was done on week- 13 samples collected overnight from the base study animals. In the sperm morphology and vaginal cytology evaluations, males were evaluated for necropsy body and reproductive tissue weights, and spermatozoal data. Females were evaluated for necropsy body weight, estrous cycle length, and percentage of cycle spent in the various stages.

Effects noted in study and corresponding doses: Hematological effects were noted at ≥ 82 mg/kg/day in females and at 281 mg/kg/day in males, but no hematological effects were found in males at 69 or 129 mg/kg/day. Females were more sensitive than males to the hematological effects. Hepatic effects were also noted at ≥ 82 mg/kg/day in females and ≥ 69 mg/kg/day for males. The hepatic effects included significantly increased levels of serum alkaline phosphatase in high dose males (452 mg/kg/day) at 3 weeks and in females at 363 and 470 mg/kg/day at 13 weeks, and in serum alanine aminotransferase in males at 452 mg/kg/day and in females at 363 and 470 mg/kg/day at week 13. Histological examination of livers revealed hepatocellular alterations (hepatocytes that stained more eosinophilic and lacked the amphophilic to basophilic granularity of the cytoplasm) at all doses (≥ 69 mg/kg/day for males and ≥ 82 mg/kg/day for females). The changes may be indications of early degeneration changes in hepatocytes. Centrilobular hepatocellular degeneration was observed in males at ≥ 281 mg/kg/day and in females at ≥ 304 mg/kg/day; and brown to green granular pigment staining strongly positive for iron in Kupffer's cell cytoplasm in males at 452 mg/kg/day and in females at ≥ 151 mg/kg/day. Renal effects were also seen in males and females. Renal effects included moderate increases in blood urea nitrogen in males at ≥ 69 mg/kg/day at week 3 and at ≥ 281 mg/kg/day at week 13 and in females at ≥ 304 mg/kg/day at week 13; increases in blood creatinine in females at ≥ 304 mg/kg/day at week 13; decreases in total blood protein in males at ≥ 281 mg/kg/day at week 13 and in females at ≥ 151 mg/kg/day at weeks 3 and 13; decreases in blood albumin in males at ≥ 281 mg/kg/day at week 13 and in females at ≥ 363 mg/kg/day at week 3 and at ≥ 304 mg/kg/day at week 13; decreased urine volume in females at ≥ 82 mg/kg/day at week 13; and increased specific gravity of the urine in

APPENDIX A

males at ≥ 69 mg/kg/day and in females at ≥ 151 mg/kg/day at week 13. However, histological examination of the kidneys and urinary bladder revealed no pathological lesions. The renal effects observed in rats may have reflected dehydration, since drinking water consumption was decreased. Thus, the 69 mg/kg/day dose in male rats is a less serious LOAEL for both hepatic and renal effects, and therefore is an appropriate dose for the derivation of the intermediate oral MRL.

69 mg/kg/day = low dose in males (LOAEL for hepatic and renal effects) - hepatocellular alteration, moderate increased blood urea nitrogen.

82 mg/kg/day = low dose in females - decreased RBC, HCT, HGB; hepatocellular alteration; decreased urine volume.

Dose endpoint used for MRL derivation: 69 mg/kg/day - hepatic effects

NOAEL LOAEL

Uncertainty factors used in MRL derivation: 1000

1 3 10 (for use of a LOAEL)

1 3 10 (for extrapolation from animals to humans)

1 3 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

If so, explain: Doses in mg/kg/day were calculated by NTP (1993) from drinking water consumption and body weight data in the experimental animals

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? If so, explain: Not applicable.

Other additional studies or pertinent information that lend support to this MRL:

In the same study by NTP (1993), groups of 10 male and 10 female B6C3F₁ mice were given targeted concentrations of 0,750, 1,500,3,000,4500, or 6,000 ppm 2-butoxyethanol in drinking water daily for 13 weeks. Actual doses were: 0, 118,223,553,676, and 694 mg/kg/day for males and 0, 185,370,676, 861, and 1,306 mg/kg/day for females. Animals were observed twice daily and weighed at the start of the studies, weekly thereafter, and at necropsy. Clinical observations were recorded weekly. Water consumption by cage was measured twice a week. Complete necropsies were performed on all animals in the base studies. The heart, right kidney, lung, thymus, and right testis were weighed, examined for gross lesions, fixed or embedded in paraffin, and stained for microscopic examination. The protocol for the 13-week studies required that tissues be examined microscopically in all control animals, animals in the highest dose group with at least 60% survivors, and all animals in the higher-dose group (inclusive of early deaths and survivors). In the sperm morphology and vaginal cytology evaluations, males were evaluated for necropsy body and reproductive tissue weights, and spermatozoal data. Females were evaluated for necropsy body weight, estrous cycle length, and percentage of cycle spent in the various stages. Clinical chemistry, urinalysis, and hematological evaluations were not performed for the mice. The only effect observed in mice was decreased body weight gain in male mice at $t \geq 53$ mg/kg/day and in female mice at ≥ 676 mg/kg/day. No hepatic or renal effects were found in the mice at ≤ 694 mg/kg/day (males) and $\leq 1,306$ mg/kg/day (females).

APPENDIX A

The only other comprehensive intermediate oral study was conducted in adult male albino rats (COBS CD (SD)BR) that were given undiluted 2-butoxyethanol by gavage in doses of 0,222,443, or 885 mg/kg/day, 5 days per week over a 6-week period (Eastman Kodak 1983; Krasavage 1986). Body weights and feed consumption were recorded. Clinical signs of toxicity and deviations from normal appearance and behavior were observed. Mortality was checked daily and dead animals were necropsied; tissues (lung, heart, thymus, kidneys, liver, spleen, brain, salivary glands, stomach, cecum, colon, duodenum, jejunum, ileum, pancreas, esophagus, adrenal glands, pituitary, thyroid, parathyroid, trachea, mesenteric lymph nodes, testes, epididymides, prostate, seminal vesicles, coagulating gland, bone marrow, tongue, and nasal cavities) were collected for histologic examination. Eyes were fixed in tinker's solution. Organ weights of liver, kidneys, heart, testes, brain, and spleen were determined. The LOAEL (serious) for hematological effects was 222 mg/kg/day, and there was no NOAEL for that effect. Hepatic and renal effects associated with the hemolytic effects occurred at 443 mg/kg/day (less serious LOAEL), but not at 222 mg/kg/day, and included hemosiderin disposition and an increase in alkaline phosphatase activity.

Agency Contact (Chemical Manager): Olivia Harris

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1) 2-2, and 2-3) and figures (2- 1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

- (1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2- 1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.
- (2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects

APPENDIX B

occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

- (3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the “System” column of the LSE table (see key number 18).
- (4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 “18r” data points in Figure 2-1).
- (5) Species The test species, whether animal or human, are identified in this column. Section 2.5, “Relevance to Public Health,” covers the relevance of animal data to human toxicity and Section 2.3, “Toxicokinetics,” contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 198 1.
- (7) System This column further defines the systemic effects These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. “Other” refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.
- (8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote “b”).
- (9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into “Less Serious” and “Serious” effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELS.
- (10) Reference The complete reference citation is given in chapter 8 of the profile.
- (11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

APPENDIX B

- (12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote “b” indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND**See Figure 2-1**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale “y” axis. Inhalation exposure is reported in mg/ m³ or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MBL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat” The key number B 8 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote “b” in the LSE table).
- (17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.
- (18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA’s Human Health Assessment Group’s upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q1*).
- (19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)		
INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3	↓	↓	↓	↓	↓		↓
4	Rat	13 wk 5d/wk 6hr/d	Resp	3 ^b	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
						11	
38	Rat	18 mo 5d/wk 7hr/d				↓ 20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

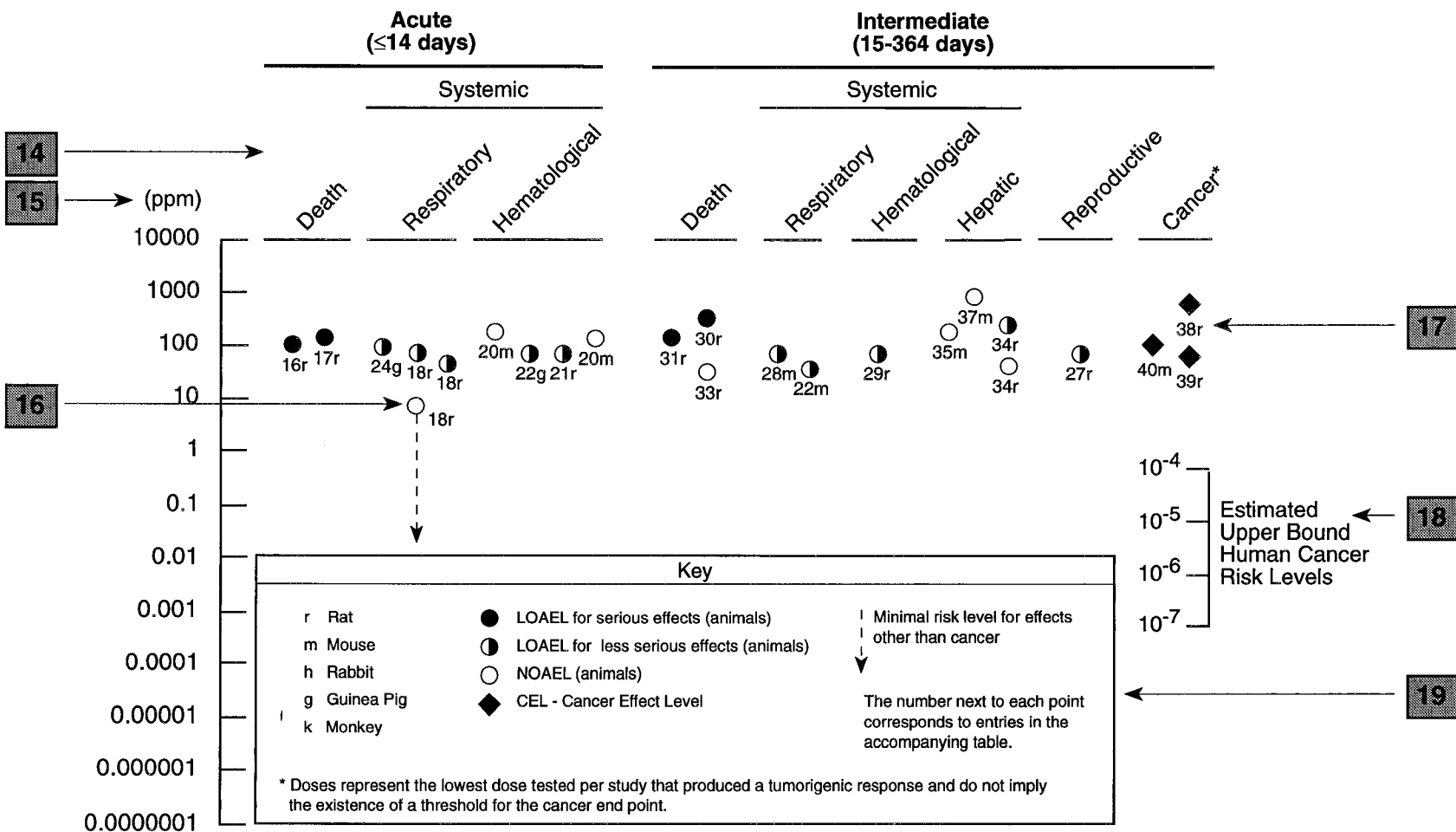
^a The number corresponds to entries in Figure 2-1.

^b an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

12

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

- 1 . What effects are known to occur in humans?
- 2 . What effects observed in animals are likely to be of concern to humans?
- 3 . What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.7, "Interactions with Other Substances," and 2.8, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot

APPENDIX B

make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a Lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C**ACRONYMS, ABBREVIATIONS, AND SYMBOLS**

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F ₁	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	<i>Federal Register</i>
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
K _d	adsorption ratio
kg	kilogram
kkg	metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient

APPENDIX C

L	liter
LC	liquid chromatography
LC _{Lo}	lethal concentration, low
LC ₅₀	lethal concentration, 50% kill
LD _{Lo}	lethal dose, low
LD ₅₀	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit

APPENDIX C

STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram