TOXICOLOGICAL PROFILE FOR DIETHYL PHTHALATE

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

June 1995

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

A Toxicological Profile for Diethyl Phthalate was released on November 1993. This edition supersedes any previously released draft or final profile.

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:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and the Environmental Protection Agency (EPA) and in support of Department of Defense information needs. 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 being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but 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.

Each toxicological profile begins with a public health statement, which describes in nontechnical language
a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, when 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 significant to protect public health will be identified by ATSDR and the EPA. The focus of the profiles is on health and toxicologic information; therefore, we have included this information in the beginning of the document.

Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance in order 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.

(C) When appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that might 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.

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, Compensationcand.Liability Act of 1980 (CERCLA or Superftmd). 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).

Foreword

This profile reflects our assessment of all relevant toxicologic testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the 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 endpoints.

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. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

A peer review panel was assembled for diethyl phthalate. The panel consisted of the following members:

1. Dr. Martin Alexander, Cornell University, Department of Agronomy, Ithaca, NY

2. Dr. Fumio Matsumura, University of California, Davis, CA

3. Dr. John Lech, Medical College of Wisconsin, Department of Pharmacology and Toxicology, Milwaukee, WI

These experts collectively have knowledge of diethyl phthalate'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

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about diethyl phthalate and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,397 sites on its National Priorities List (NPL). Diethyl phthalate has been found in at least 248 of these sites, one of which is located in Guam. However, we do not know how many of the 1,397 NPL sites have been evaluated for diethyl phthalate. As EPA evaluates more sites, the number of sites at which diethyl phthalate is found may change. This information is important for you to know because diethyl phthalate may cause harmful health effects and because these sites are potential or actual sources of human exposure to diethyl phthalate.

When a chemical 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 as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous chemical such as diethyl phthalate, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life-style, and state of health.

1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS DIETHYL PHTHALATE?

Diethyl phthalate is a man-made colorless liquid with a slight aromatic odor and a bitter, disagreeable taste. Trade names include neantine, peilatinol A, and solvanol. Diethyl phthalate is manufactured for many uses. It is commonly used to make plastics more flexible. Because diethyl phthalate is not a part of the chain of chemicals (polymers) which makes up the plastics, it can be released fairly easily from these products. These plastics are found in products such as toothbrushes, automobile parts, tools, toys, and food packaging. Diethyl phthalate is also used in cosmetics, insecticides, and aspirin. For more information on the chemical and physical properties of diethyl phthalate, see Chapter 3. For more information on its production and use, see Chapter 4.

1.2 WHAT HAPPENS TO DIETHYL PHTHALATE WHEN IT ENTERS THE ENVIRONMENT?

Diethyl phthalate may enter the environment in industrial waste waters, by evaporation into the air from disposal sites, directly from consumer products, from the burning of plastic products, and by leaking from landfills into soil or water including groundwater. In air, diethyl phthalate may break down into other products. It may also be deposited on the ground or in water by rain. Diethyl phthalate may also enter the environment by sticking onto dust particles. If released into water, diethyl phthalate may travel great distances in swiftly moving rivers. In more slowly moving waters, microorganisms in the water or sediment may break down some of the diethyl phthalate into nontoxic products. -Sewage bacteria from industrial facilities may break down diethyl phthalate in waste waters. In soils containing organic matter (matter with high levels of carbon), diethyl phthalate may stick to particles where it may eventually break down. If there is little organic matter in the soil, diethyl phthalate may move down through the soil and enter the groundwater. Many microorganisms are able to break down diethyl phthalate to carbon dioxide and other harmless

products. Small amounts of diethyl phthalate can build up in animals that live in water, such as fish and oysters. For further information on what happens to diethyl phthbalate when it enters the environment, see Chapters 4 and 5.

1.3 HOW MIGHT I BE EXPOSED TO DIETHYL PHTHALATE?

You may be exposed to diethyl phthalate in consumer products and plastics. You may also be exposed during the manufacturing or disposal of products that contain diethyl phthalate. Most exposure will result from inhalation of contaminated air or swallowing of contaminated drinking water or foods. The measured levels of diethyl phthalate in air, water, and soil are generally quite low. For example, diethyl phthalate has been measured at hazardous waste sites in the groundwater at 0.0125 parts of diethyl phthalate per million parts (ppm) of water, in surface water at 0.0121 ppm, and in soil at 0.039 ppm (on a weight basis, a part per million is equivalent to one unit of weight, such as one gram, of a chemical, in l,000,000 grams of a medium, such as water or soil). Diethyl phthalate has been found in drinking water at concentrations of 0.00001-0.0046 ppm, in industrial waste waters at 0.00001-0.060 ppm, in river waters at 0.00006-0.044 ppm, and in sediments from other large bodies of water (Chesapeake Bay and Gulf of Mexico) at up to 0.042 ppm. The amount of diethyl phthalate in soil is unknown. However, diethyl phthalate will probably be rapidly decomposed by soil bacteria, so that little will be taken up into plants. Diethyl phthalate has been measured in indoor air (in a telephone switching office) at 0.00018-0.00022 ppm and in outdoor air (Newark, New Jersey) at 0.00004-0.00006 ppm. Fish taken from contaminated waters had up to about 2 ppm of diethyl phthalate in their tissues. Oysters contained up to about 1 ppm. Diethyl phthalate in plastic packaging may get into food and has been found in packaged food (quiche) at concentrations of about 2-5 ppm. The daily human intake of diethyl phthalate has been estimated to be 4 milligrams (mg) based on food intake, but the annual exposure from drinking contaminated drinking water has been estimated to be quite low (0.0058 mg/year/person).

Occupational exposure to diethyl phthalate is possible as a result of its use in plastics and other products such as cosmetics and insect repellents. The National Occupational Exposure Survey estimated that over 239,000 employees could potentially be exposed to diethyl phthalate in the workplace. Diethyl phthalate was found in plants that manufacture rubber products at concentrations up to 0.0013 ppm. For further information on how you can be exposed to diethyl phthalate, see Chapter 5.

1.4 HOW CAN DIETHYL PHTHALATE ENTER AND LEAVE MY BODY?

Diethyl phthalate can enter your body when you breathe air, drink water, or eat food containing it. It can also enter your body through your skin. It is possible that exposure could occur near hazardous waste sites, at manufacturing facilities, or through the use of consumer products containing the substance. If you get it on your skin, your body will probably absorb only a small amount of it. We do not know how much you will absorb if you breathe or eat it. Once it enters your body, it breaks down into other chemicals, some of which are harmful. Diethyl phthalate and its breakdown products will leave your body mostly in the urine within about 2 days. Only small amounts of the compound or its breakdown products will remain in the tissues. For more information on how diethyl phthalate can enter and leave your body, see Chapter 2.

1.5 HOW CAN DIETHYL PHTHALATE AFFECT MY HEALTH?

No information is available regarding the possible effects caused by diethyl phthalate if you breathe, eat, drink, or have skin contact with it. Because no studies involving humans exposed exclusively to diethyl phthalate are available, we must rely on studies in laboratory animals. Furthermore, there is no information on the effects of breathing diethyl phthalate in laboratory animals. Diethyl phthalate has caused death in animals given very high doses by mouth, but brief oral exposures to lower doses caused no harmful effects. One effect found

in animals that ate high doses of diethyl phthalate for long periods of time was a decrease in weight gain. This effect may have occurred because they ate less food, or because they excreted more of the food they ate. The livers and kidneys of these animals were larger than normal, but not from any harmful effect. Other studies noted the presence of an extra rib in rat fetuses whose mothers were given very high dietary levels of diethyl phthalate, but this effect is not considered harmful by all scientists.

Diethyl phthalate is not known to cause cancer in humans or animals. Unlike other phthalates such as di(2-ethylhexyl) phthalate, diethyl phthalate does not appear to affect the ability of male animals to father babies (see ATSDR toxicological profile for di[2-ethylhexyl] phthalate for more information on this chemical). However, a decrease occurred in the number of live babies born to female animals that were exposed to diethyl phthalate throughout their lives. Some birth defects occurred in newborn rats whose mothers received high doses (approximately 3 g/kg) of diethyl phthalate by injection during pregnancy. However, humans are not exposed to diethyl phthalate this way, and no information is available on whether this chemical can cause birth defects when given by mouth.

Diethyl phrhalate can be mildly irritating when applied to the skin of animals. It can also be slightly irritating when put directly into the eyes of animals. We have no information on the health effects of diethyl phthalate when applied to the skin for long periods of time. For more information on the health effects of diethyl phthalate, please refer to Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO DIETHYL PHTHALATE?

Chemical tests are available to determine diethyl phthalate levels in semen, fat, and kidney tissues. See Chapters 2 and 6 for more information.

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

The government has developed regulations and guidelines for diethyl phthalate. These are designed to protect the public from the possible harmful health effects of the chemical. Under laws that relate to Superfund sites, EPA has identified diethyl phthalate as a hazardous substance. This decision is based primarily on the large number of Superfund sites where diethyl phthalate is found.

The Occupational Safety and Health Administration (OSHA) regulates levels of diethyl phthalate in the workplace. The maximum amount of diethyl phthalate allowed in workroom air during an 8-hour workday, 40-hour workweek, is 5 milligrams per cubic meter (mg/m^3). See Chapter 7 for more information on regulations and guidelines. The National Institute for Occupational Safety and Health (NIOSH) also recommends a similar maximum air concentration of 5 mg/m^3 for workplace exposure.

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:

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

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. These clinics specialize in the recognition, evaluation, and treatment of illnesses resulting from exposure to hazardous substances.

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 diethyl phthalate and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and describes levels of significant exposure for diethyl phthalate based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals 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 a figure. The points in the figure 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. These distinctions are intended to help-users of the documents identify levels of exposure at which adverse health effects start to appear. They should also help to determine 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 tables and figures may differ depending on the user’s perspective. For example, physicians concerned with the interpretation of clinical findings in

exposed persons may be interested in levels of exposure associated with “serious” effect. Public health officials and project managers 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 (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability and extrapolation of data from laboratory animals and humans.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), 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.

2.2.1 Inhalation Exposure

No studies were located regarding the following health effects in humans or animals following inhalation exposure to diethyl phthalate.

2.2.1.1 Death

2.2.1.2 Systemic Effects

2.2.1.3 Immunological and Lymphoreticular Effects

2.2.1.4 Neurological Effects

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals following inhalation exposure to diethyl phthalate.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans following oral exposure to diethyl phthalate.

The lowest lethal doses of diethyl phthalate in rabbits and guinea pigs administered the compound by gavage were determined to be 4,000 and 5,000 mg/kg, respectively (Smyth and Smyth 1931). However, this study is limited in that only two to six animals were tested at each dose level and no control data were presented. Furthermore, neither the clinical signs exhibited by the animals nor the cause(s) of death were stated. No deaths were observed when diethyl phthalate was incorporated into the diet of mice for 2 weeks at doses of up to 6,500 mg/kg/day. Thus, based on this information, it would appear that diethyl phthalate is relatively nonlethal to orally exposed experimental animals.

2.2.2.2 Systemic Effects

No studies were located regarding dermal effects in humans or animals following oral exposure to diethyl phthalate.

2. HEALTH EFFECTS

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

Respiratory Effects. No studies were located regarding respiratory effects in humans following oral exposure to diethyl phthalate. Two-to-16-week dietary administration of diethyl phthalate, at concentrations up to 3,710 mg/kg/day, had no effect on the gross or microscopic pathology of the lungs or trachea in rats (Brown et al. 1978).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following oral exposure to diethyl phthalate. Two-to-16-week dietary administration of diethyl phthalate, at concentrations up to 3,710 mg/kg/day, had no effect on the gross or microscopic pathology of the hearts or aorta in rats. Administration of 3,160 mg/kg/day to male rats resulted in a statistically significant ($p<0.01$) increase in heart weight (Brown et al. 1978).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following oral exposure to diethyl phthalate. Two-to-16-week dietary administration of high concentrations of diethyl phthalate resulted in enlarged stomachs, small intestines, and/or caecums. No evidence of histological damage was found in any gastrointestinal tissue. The investigators did not consider the effects treatment-related (Brown et al. 1978).

Hematological Effects. No studies were located regarding hematological effects in humans following oral exposure to diethyl phthalate. A statistically significant increase in erythrocyte counts was reported in male rats receiving 3,160 mg/kg/day (5% in diet) diethyl phthalate in the diet for 6 weeks. However, this change was no longer apparent after 16 weeks of dietary administration. In addition, no treatment-related effects were noted in packed cell volume, reticulocyte counts, or leukocyte counts in male or female rats in this study (Brown et al. 1978).

TABLE 2-1. Levels of Significant Exposure to Diethyl Phthalate - Oral

Key[a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)		LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Systemic								
1	Rat CD	2 wk ad lib (F)	Resp	3160 3710	M F			Brown et al. 1978
			Cardio	3160 3710	M F			
			Gastro	3160 3710	M F			
			Hemato	3160 3710	M F			
			Musc/skel	3160 3710	M F			
			Hepatic	3160 3710	M F			
			Renal	3160 3710	M F			
			Endocr	3160 3710	M F			
			Ocular	3160 3710	M F			
			Bd Wt	3160 3710	M F			
2	Rat Sprague-Dawley	4 d 1x/d (GO)	Bd Wt	1600	M			Foster et al. 1980
3	Mouse Cd-1	14 d ad lib (F)	Bd Wt	3250		6500	(> 10% decrease in body weight)	NTP 1984

TABLE 2-1. Levels of Significant Exposure to Diethyl Phthalate - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
Immuno/Lymphoret							
4	Rat CD	2 wk ad lib (F)		3160 M 3710 F			Brown et al. 1978
Neurological							
5	Rat CD	2 wk ad lib (F)		3160 M 3710 F			Brown et al. 1978
Reproductive							
6	Rat CD	2 wk ad lib (F)		3160 M 3710 F			Brown et al. 1978
7	Rat Sprague-Dawley	1-4 d 1x/d (GO)		1600 M			Foster et al. 1983
8	Rat Wistar	10 d 1x/d (GO)		1600 M			Gray and Butterworth 1980
9	Rat Wistar	1 x/d 2d (F)			2000 [b] M (mitochondrial swelling with focal dilation; Leydig cell SER vesiculation)		Jones et al. 1993
10	Rat Wistar	1 wk ad lib (F)		1000 M			Oishi and Hiraga 1980

TABLE 2-1. Levels of Significant Exposure to Diethyl Phthalate - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)		LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)	Reference
Developmental									
11	Rat Sprague-Dawley	10 d Gd 6-15 ad lib (F)		1910	F	3210	F (increased incidence of supernumerary ribs)		Field et al. 1993
12	Mouse CD-1	6 d Gd 6-13 1x/d (GO)		4500	F				Hardin et al. 1987
INTERMEDIATE EXPOSURE									
Systemic									
13	Rat CD	16 wk ad lib (F)	Resp	3160	M				Brown et al. 1978
				3710	F				
			Cardio	3160	M				
				3710	F				
			Gastro	3160	M				
				3710	F				
			Hemato	3160	M				
				3710	F				
			Musc/skel	3160	M				
				3710	F				
			Hepatic	3160	M				
				3710	F				
			Renal	3160	M				
				3710	F				
			Endocr	3160	M				
				3710	F				
			Ocular	3160	M				
				3710	F				
			Bd Wt	3160	M				
				3710	F				

TABLE 2-1. Levels of Significant Exposure to Diethyl Phthalate - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
14	Rat F-344	3 wk (F)	Hepatic		1753 [c] M (slight increase in liver weights and activity of peroxisomal enzymes; mild peroxisomal proliferation)		Moody and Reddy 1978
15	Mouse CD-1	NS ad lib (F)	Bd Wt	1625 M 3250 F	3250 M (body weight gain inhibition of > 10%)		Lamb et al. 1987
Immuno/Lymphoret							
16	Rat CD	16 wk ad lib (F)		3160 M 3710 F			Brown et al. 1978
Neurological							
17	Rat CD	16 wk ad lib (F)		3160 M 3710 F			Brown et al. 1978
Reproductive							
18	Rat CD	16 wk ad lib (F)		3160 M 3710 F			Brown et al. 1978
19	Mouse CD-1	NS ad lib (F)				3250 (< number of pups)	Lamb et al. 1987

[a]The number corresponds to entries in Figure 2 -1.

[b]Used to derive an acute oral Minimal Risk Level (MRL) of 7 mg/kg/day; dose was divided by an uncertainty factor of 300 (3 for the conversion of a minimal LOAEL to a NOAEL, 10 for interspecies extrapolation, and 10 for human variability).

[c]Used to derive an intermediate oral MRL of 6 mg/kg/day; dose was divided by an uncertainty factor of 300 (3 for the conversion of a minimal LOAEL to a NOAEL, 10 for interspecies extrapolation, and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = female(s); Gastro = gastrointestinal; (GO) = gavage in oil; Gd = gestation day; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed- adverse-effect level; M = male(s); Musc/skel = musculoskeletal; NOAEL = no-observed- adverse-effect level; NS = not specified; Resp = respiratory; SER = smooth endoplasmic reticulum; wk = week(s); x = time(s)

Figure 2-1. Levels of Significant Exposure to Diethyl Phthalate – Oral (continued)

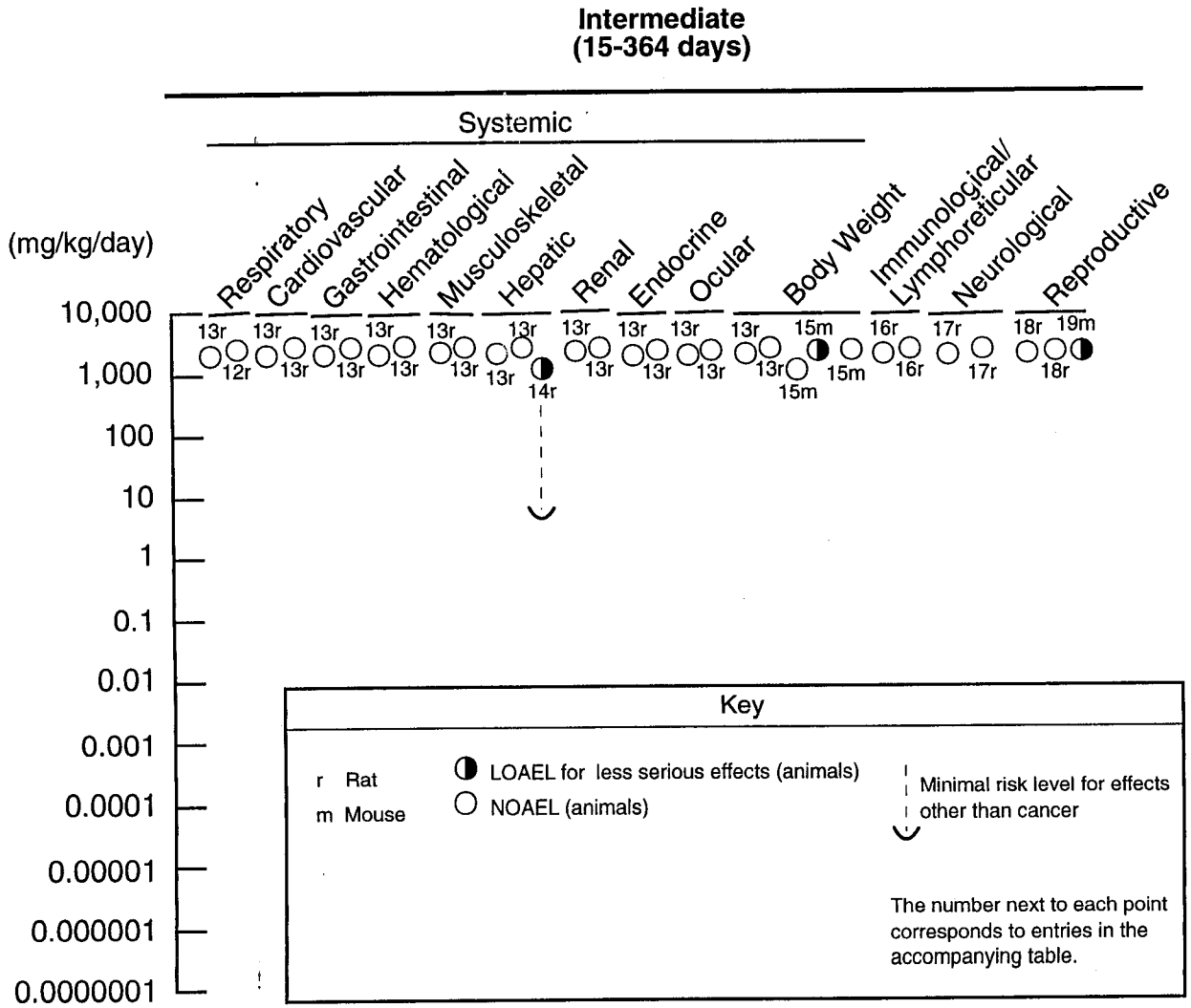
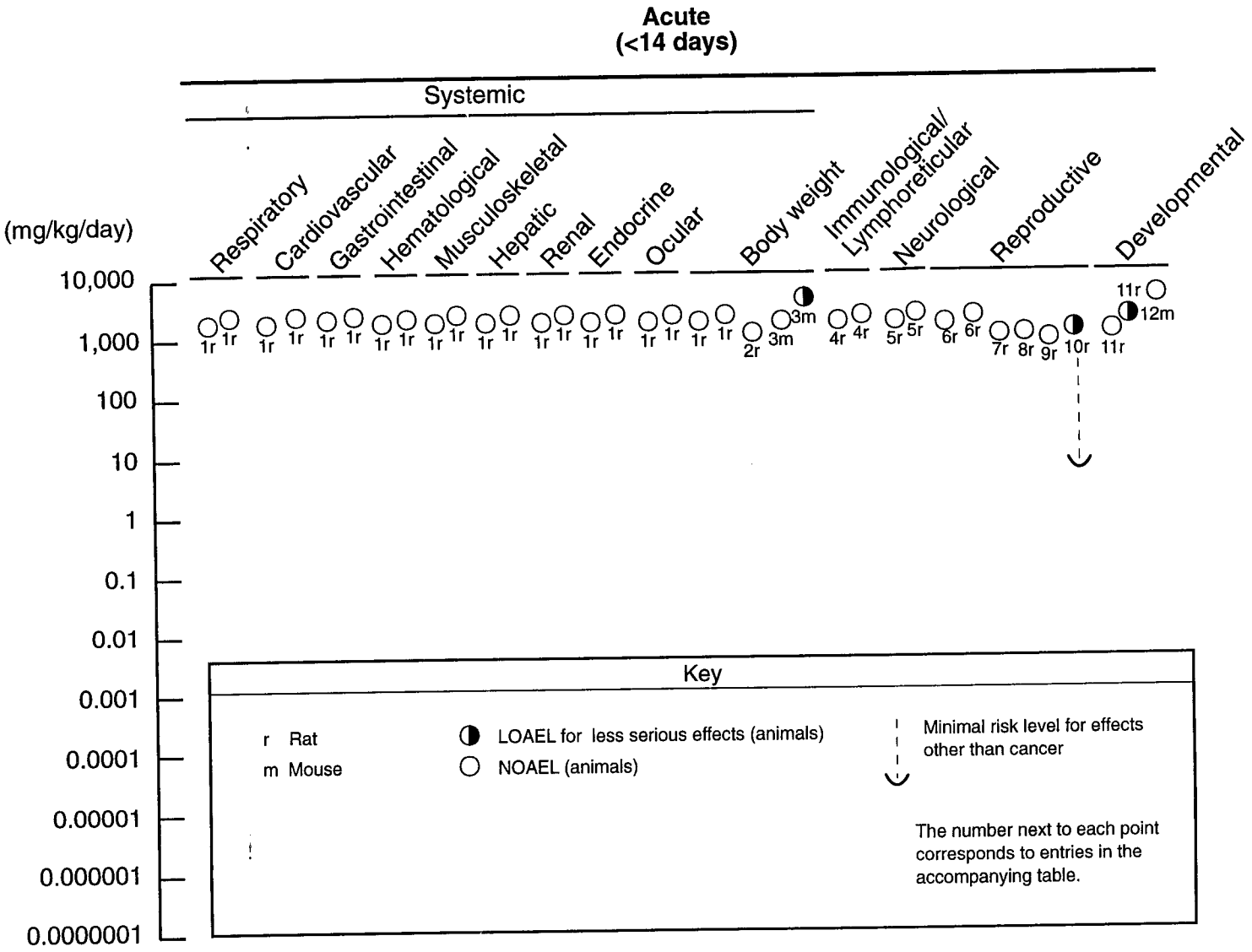


Figure 2-1. Levels of Significant Exposure to Diethyl Phthalate – Oral



2. HEALTH EFFECTS

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following oral exposure to diethyl phthalate. Two-to-l6-week dietary administration of diethyl phthalate, at concentrations up to 3,710 mg/kg/day, had no effect on the gross or microscopic pathology of skeletal muscle in rats (Brown et al. 1978).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to diethyl phthalate. A number of studies have reported increases in absolute and relative liver weights in animals administered up to 3,710 mg/kg/day diethyl phthalate in the diet for an acute exposure duration (Brown et al. 1978; Oishi and Hiraga 1980). However, in the absence of biochemical, functional, or histopathological evidence of liver damage, the toxicological significance of these changes in liver weight is not known. Only slight, but statistically significant, increases in liver weight, hepatic peroxisome, and hepatic catalase and camitine acetyltransferase activities occurred in rats administered 1,753 mg/kg/day diethyl phthalate in the diet for 3 weeks (Moody and Reddy 1978). These changes were minor compared to changes observed after dietary administration of di-(2-ethylhexyl)phthalate, di-(2-ethylhexyl)adipate, or di-(2-ethylhexyl)sebacate. Nevertheless, the observed changes are considered a less serious LOAEL and were used to derive an intermediate-duration MRL of 6 mg/kg/day, as described in Section 2.4.

Fatty degeneration and slight vacuolation were noted in the liver of some animals fed diethyl phthalate for up to 16 weeks (Brown et al. 1978). However, although no incidence data were provided, the investigators stated that these changes were not dose related. A dose-related increase in the incidence of congestion, cloudy swelling, and scant, moderate, or abundant glycogen was noted in guinea pigs administered 250-1,000 mg/kg/day diethyl phthalate in the feed for l-3 months (Smyth and Smyth 1932). This study is limited, however, in that only two to four animals were tested at each dose.

Based on the available information, it appears that while diethyl phthalate can induce an increase in relative liver weight in experimental animals, the absence of any treatment-related biochemical, functional, or histopathological changes in the liver suggests that the increase in liver weight may be due to exposure to high oral concentrations rather than to a direct toxic effect of diethyl phthalate.

2. HEALTH EFFECTS

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to diethyl phthalate.

An increase in relative kidney weight was observed in male rats administered 5% diethyl phthalate in the diet for 2 weeks, and in male and female rats administered 5% diethyl phthalate in the diet for 16 weeks (Brown et al. 1978). The approximate daily intakes (listed by the authors) were 3,160 mg/kg/day for male rats and 3,710 mg/kg/day for female rats. There was no evidence that these organ weight changes were accompanied by any biochemical, functional, or histopathological renal damage. Therefore, the toxicological significance of this change in kidney weight is not known.

Congestion, cloudy swelling of the tubules, and desquamation were noted in guinea pigs administered 250-1,000 mg/kg/day diethyl phthalate in the feed for l-3 months (Smyth and Smyth 1932). This study is limited, because only three or four animals were tested at each dose.

Based on the available information, it appears that while diethyl phthalate can induce an increase in relative kidney weight in experimental animals, the absence of any reliable treatment-related biochemical, functional, or histopathological changes in the kidney suggests that the increase in kidney weight was probably not due to a direct toxic effect of diethyl phthalate.

Endocrine Effects. No studies were located regarding endocrine effects in humans following oral exposure to diethyl phthalate. Two-to-16-week dietary administration of diethyl phthalate, at concentrations up to 3,710 mg/kg/day, had no effect on the gross or microscopic pathology of the pituitary, adrenals, thyroid, or pancreas in rats. Relative organ weights of the adrenals, pituitary, and thyroid were slightly to moderately elevated at 3,160 mg/kg/day in males (Brown et al. 1978).

Ocular Effects. No studies were located regarding ocular effects in humans following oral exposure to diethyl phthalate. Two-to-16-week dietary administration of diethyl phthalate, at concentrations up to 3,710 mg/kg/day, had no effect on the gross or microscopic pathology of the eye (Brown et al. 1978).

Body Weight. No studies were located regarding body weight changes in humans following oral exposure to diethyl phthalate.

A number of studies have reported significant (>l0%) decreases in body weight gain in experimental animals after acute- and intermediate-duration dietary exposure (Brown et al. 1978; Lamb et al. 1987; NTP 1984). In at least one study, the results of a concurrent paired-feeding experiment indicated that the inhibition was primarily attributable to lower food consumption and/or poorer food utilization, rather than to a direct toxic action of diethyl phthalate (Brown et al. 1978). In a continuous breeding study with mice, dietary administration of the equivalent of 3,250 mg/kg/day was associated with a 47% weight gain inhibition (Lamb et al. 1987).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans following oral exposure to diethyl phthalate. Two-to-16-week dietary administration of diethyl phthalate, at concentrations up to 3,710 mg/kg/day, had no effect on the gross or microscopic pathology of (unspecified) lymph nodes or the thymus (Brown et al. 1978).

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans following oral exposure to diethyl phthalate. Two-to-16-week dietary administration of diethyl phthalate, at concentrations up to 3,710 mg/kg/day, had no effect on the gross or microscopic pathology of the brain or the sciatic nerve (Brown et al. 1978). Exposure to 3,160 mg/kg/day (males) or 3,710 mg/kg/day (females) resulted in increased relative brain weights (Brown et al. 1978).

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to diethyl phthalate.

2. HEALTH EFFECTS

Several investigators have studied the effects of diethyl phthalate on male reproductive function in rats since other phthalic acid esters have been shown to be toxic to the male reproductive system (ATSDR 1989; Foster et al. 1980, 1983; Gray and Butterworth 1980; Oishi and Hiraga 1980). Testicular and accessory gland weight and histopathology were unaffected by treatment of male rats with diethyl phthalate at doses up to 1,600 mg/kg/day (Foster et al. 1980; Gray and Butterworth 1980; Oishi and Hiraga 1980). In addition, diethyl phthalate had no effect on progesterone binding to testes microsomes, testicular cytochrome P-450 content, or testicular steroidogenic enzyme activity, whereas other phthalates known to cause testicular toxicity have induced changes in these parameters (Foster et al. 1983). The authors concluded that the lack of effect on these parameters is consistent with the lack of morphological effects on the testes reported in other studies.

Acute administration of 2,000 mg/kg/day diethyl phthalate produced ultrastructural evidence of Leydig cell mitochondrial swelling, and both focal dilatation and vesiculation of the smooth endoplasmic reticulum (Jones et al. 1993). These findings are considered a less serious LOAEL and were used to derive an acute oral MRL of 7 mg/kg/day (see Section 2.4).

In a continuous breeding study in CD-l mice, dietary administration of 2.5% diethyl phthalate (>99% pure) (3,250 mg/kg/day) produced physiological effects in F_1 parental animals and significantly decreased the number of live pups per litter (Lamb et al. 1987). No adverse effects on the physiology, fertility, or reproductive performance of the F_0 generation animals were observed. The F_0 mice were fed diets containing the test compound at concentrations of 0, 325, 1,625, or 3,250 mg/kg daily during premating, mating, gestation, and lactation; the F_1 generation animals received 0 or 3,250 mg/kg/day on the same regimen.

The parental toxicity in the F_1 generation was evidenced by a significant decrease in body weight, increased prostate weight in males, and increased liver and pituitary weights in females. However, histological findings in the liver and pituitary were not reported, rendering the toxicological significance of a change in these organ weights uncertain. Although a significant decrease in sperm concentration occurred in the males, no adverse effect on the fertility was observed. The total number of live pups per litter in the F_1 generation was significantly lower by 14% in the test group compared to the controls. The study limitations include a lack of data on the histopathological findings of the

tissues and failure to assess the effects of the test compound on the F_1 generation at the two lower doses. Data on the F, generation showed an increase in the number of live pups per litter at the low doses. As a result, no NOAEL was established.

Administration of up to a dose equivalent of 3,710 mg/kg/day diethyl phthalate was associated with no gross or microscopic evidence of histopathological damage to the gonads, uterus, or the prostate and seminal vesicles of rats. Relative testes weights were significantly elevated at a dose equivalent of 3,160 mg/kg/day (Brown et al. 1978).

The highest NOAEL value and the LOAEL value for reproductive effects for each species and duration category are recorded in Table 2-l and plotted in Figure 2-1.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to diethyl phthalate.

A study in mice reported no significant evidence of maternal toxicity or neonatal developmental effects due to oral administration of 4,500 mg/kg/day on gestation days 6-13 (Hardin et al. 1987). Newborn mice were evaluated for survival, birth weight, and weight gain. A limitation of this study was that these results were determined by use of a proposed short-term in *vivo* developmental toxicity assay, and no comparison of this method to conventional assays was available. In rats, dietary administration of up to 2.5% diethyl phthalate (1,910 mg/kg/day) produced no embryonic or fetotoxic effects. At a dietary level of 5% (3,210 mg/kg/day), treated embryos had an increased number of skeletal variations, particularly rudimentary (supernumerary) ribs (Field et al. 1993). However, the significance of this finding is obscured by the high incidence of skeletal variations in the controls and the reduced food and water consumption of the high-dose dams early in gestation.

The NOAEL value and LOAEL value for developmental effects after acute exposure to diethyl phthalate are recorded in Table 2-1 and plotted in Figure 2-l.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to diethyl phthalate.

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals following oral exposure to diethyl phthalate.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans following dermal exposure to diethyl phthalate. At daily application doses of up to 100 μL (mice) or 300 μL (rats), equivalent to 772 mg/kg/day (mice) and 855 mg/kg/day (rats), diethyl phthalate did not produce an increased mortality incidence when administered 5 days per week for 2 years (NTP 1993 [board draft]).

2.2.3.2 Systemic Effects

No studies were located regarding musculoskeletal effects in humans or animals following dermal exposure to diethyl phthalate.

The highest NOAEL values and all reliable LOAEL values for systemic effects for each species and duration category are recorded in Table 2-2.

TABLE 2-2. Levels of Significant Exposure to Diethyl Phthalate - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
ACUTE EXPOSURE						
Systemic						
Rabbit New Zealand	once	Ocular	0.1m washed			Dear and Jassup 1978
Rabbit New Zealand	once	Ocular		0.1mL not washed	(minimally irrating)	Dear and Jassup 1978
Immuno/Lymphoret						
Human	5x		0.1 mL			Greif 1967
INTERMEDIATE EXPOSURE						
Systemic						
Rat F344	4 w 5d/w	Resp	1715			NTP 1993
		Cardio	1715			
		Gastro	1715			
		Hemato	1715			
		Hepatic	1715			
		Renal	1715			
		Endocr	1715			
		Derm	1715			
		Bd Wt	1715			
Mouse B6C3F1	4 w 5d/w	Resp	3740			NTP 1993
		Cardio	3740			
		Gastro	3740			
		Hepatic	3740			
		Renal	3740			
		Endocr	3740			
		Derm	3740			
		Bd Wt	3740			

TABLE 2-2. Levels of Significant Exposure to Diethyl Phthalate - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
Rat B6C3F1	103 w 5d/w	Resp	772			NTP 1993
		Cardio	772			
		Gastro	772			
		Hemato	772			
		Hepatic	772			
		Renal	772			
		Endocr	772			
		Derm	772			
		Bd Wt	772			
Immuno/Lymphoret						
Rat F344/N	103 w 5d/w		855			NTP 1993
Mouse B6C3F1	103 w 5d/w		772			NTP 1993
Neurological						
Rat F344/N	103 w 5d/w		855			NTP 1993
Mouse B6C3F1	103 w 5d/w		772			NTP 1993
Reproductive						
Rat F344/N	103 w 5d/w		855			NTP 1993
Mouse B6C3F1	103 w 5d/w		772			NTP 1993

TABLE 2-2. Levels of Significant Exposure to Diethyl Phthalate - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
Immuno/Lymphoret						
Rat F344	4 w 5d/w		1715			NTP 1993
Mouse B6C3F1	4 w 5d/w		3740			NTP 1993
Neurological						
Rat F344	4 w 5d/w		1715			NTP 1993
Mouse B6C3F1	4 w 5d/w		3740			NTP 1993
Reproductive						
Rat F344	4 w 5d/w		1715			NTP 1993
Mouse B6C3F1	4 w 5d/w		3740			NTP 1993
CHRONIC EXPOSURE						
Systemic						
Rat F344/N	103 w 5d/w	Resp	855			NTP 1993
		Cardio	855			
		Gastro	855			
		Hemato	855			
		Hepatic	855			
		Renal	855			
		Endocr	855			
		Derm	855			
		Bd Wt	855			

TABLE 2-2. Levels of Significant Exposure to Diethyl Phthalate - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
				Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Cancer						
Rat F344/N	103 w 5d/w					NTP 1993
Mouse B6C3F1	103 w 5d/w					NTP 1993

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Derm = dermal; Endocr = endocrine; Gastro = gastrointestinal; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse effect; NOAEL = no-observed- adverse-effect level; Resp = respiratory; wk = week(s); x = time(s)

Respiratory Effects. No studies were located regarding respiratory effects in humans following dermal exposure to diethyl phthalate.

Repeated dermal administration of diethyl phthalate had no adverse effects on lung histopathology in rats or mice exposed for 4 weeks or 2 years (NTR 1993 [board draft]).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following dermal exposure to diethyl phthalate.

Repeated dermal administration of diethyl phthalate had no adverse effects on heart histopathology in rats or mice exposed for 4 weeks or 2 years (NTP 1993 [board draft]).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following dermal exposure to diethyl phthalate.

Repeated dermal administration of diethyl phthalate had no adverse effects on the histopathology of the esophagus, gallbladder (mouse only), large intestine, small intestine, stomach, or bladder in rats or mice exposed for 4 weeks or 2 years (NTP 1993 [board draft]).

Hematological Effects. No studies were located regarding hematological effects in humans following dermal exposure to diethyl phthalate.

The results of studies in rats and mice indicated no adverse effects on standard hematological parameters after repeated dermal application of 100% diethyl phthalate (NTR 1993 [board draft]).

Hepatic Effects. No studies were located regarding hepatic effects in humans following dermal exposure to diethyl phthalate.

2. HEALTH EFFECTS

Repeated dermal administration of diethyl phthalate had no adverse effects on liver histopathology in rats or mice exposed for 4 weeks or 2 years (NTP 1993 [board draft]). In 4-week studies, administration of diethyl phthalate did result in increased relative liver weights in both sexes of rats and in female mice. However, no adverse effects on clinical indices of liver function were noted (NTP 1993 [board draft]).

Renal Effects. No studies were located regarding renal effects in humans following dermal exposure to diethyl phthalate.

Repeated dermal administration of diethyl phthalate had no adverse effects on kidney histopathology in rats or mice exposed for 4 weeks or 2 years (NTP 1993 [board draft]). In 4-week studies, administration of diethyl phthalate did result in increased relative kidney weights in both sexes of rats. However, no adverse effect on clinical indices of kidney function were noted (NTP 1993 [board draft]).

Dermal Effects. No studies were located regarding dermal effects in humans following dermal exposure to diethyl phthalate.

Diethyl phthalate was shown to be very slightly or slightly irritating when applied repeatedly to the intact or abraded skin, respectively, of an unidentified species (Dow Chemical 1952). However, the criteria to judge irritation were not specified in this study, and none of the protocol details were provided. Other data indicate that chronic dermal diethyl phthalate administration is associated with mild, nonadverse dermal acanthosis in rats (NTP 1993 [board draft]). One study reported that diethyl phthalate caused intradermal irritation evidenced by the presence of inflammation at the site of injection in the skin.of rabbits (Galley et al. 1966).

Ocular Effects. No studies were located regarding ocular effects in humans following dermal exposure to diethyl phthalate.

Ocular irritation tests conducted in rabbits indicate that diethyl phthalate is not a primary ocular irritant (Dear and Jassup 1978; Lawrence et al. 1975). The compound caused minimal irritation when applied to the eye without washing, and was practically non-irritating when the eye was washed after instillation (Dear and Jassup 1978).

Body Weight Effects. No studies were located regarding body weight effects in humans following dermal exposure to diethyl phthalate.

In 2-year rat dermal toxicity studies, diethyl phthalate produced slight body weight gain decrements in male and female rats. The equivalent doses administered were 285 and 855 mg/kg/day. Diethyl phthalate had no effect on body weight gain in 4-week rat and mouse studies or in 2-year mouse studies (NTP 1993 [board draft]).

2.2.3.3 Immunological and Lymphoreticular Effects

In a factory that produces shoes from polyvinyl chloride granulate (which contains a compound the authors called dioctyl phthalate, but which is probably di-[2-ethylhexyllphthalate), 30 workers with dermatitis and 30 workers without dermatitis were patch tested with diethyl phthalate and compared with 30 controls that had no known exposure to polyvinyl chloride or phthalates (Vidovic and Kansky 1985). One worker of the 30 with dermatitis and 1 of the 30 without dermatitis responded positively with an allergic contact response to diethyl phthalate. None of the controls had a positive response. The authors concluded that the results in the exposed worker populations indicate that the phthalates are sensitizers, and that the positive reaction to diethyl phthalate was most likely due to cross-sensitization with dioctyl phthalate since very little diethyl phthalate is present in polyvinyl chloride (Vidovic and Kansky 1985). In a skin patch test designed to maximize sensitization, none of 25 healthy adult volunteers showed a positive reaction to diethyl phthalate (Greif 1967).

The NOAEL and LOAEL values for immunological or lymphoreticular effects in humans following dermal exposure are recorded in Table 2-2.

Repeated dermal administration of diethyl phthalate had no adverse effects on the histopathology of the spleen, thymus, or lymph nodes or on thyroid weight in rats or mice exposure for 4 weeks or 2 years (NTP 1993 [board draft]).

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans following dermal exposure to diethyl phthalate. In 4-week and 2-year studies with rats and mice, diethyl phthalate had no adverse effect on the histopathology or weight of the brain (NTP 1993 [board draft]). These NOAEL values are recorded in Table 2-2.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following dermal exposure to diethyl phthalate.

In 4-week and 2-year studies with rats and mice, diethyl phthalate had no adverse effect on the histopathology of male or female reproductive organs (NTP 1993 [board draft]). These NOAEL values are recorded in Table 2-2.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following dermal exposure to diethyl phthalate.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following dermal exposure to diethyl phthalate.

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans following dermal exposure to diethyl phthalate.

The results of a board draft study indicated that male and female rats receiving 100 or 300 µL diethyl phthalate (approximately 285 mg/kg/day or 855 mg/kg/day), applied to the intrascapular skin 5 days per week for 2 years, did not develop any evidence of carcinogenic activity. Equivocal evidence of carcinogenicity was found in both sexes of mice dermally exposed to up to 30 µL diethyl phthalate/day, 5 days per week for 2 years. The incidences of combined hepatocellular adenoma/carcinoma in the male mice dosed with 0, 7.5, 15, and 30 µL/day (corresponding to 0, 193, 386, and 772 mg/kg/day) were 9/50, 14/50, 14/50, and 18/50, respectively. The corresponding incidences in the female mice were 7/50, 16/51, 19/50, and 12/50, respectively (NTP 1993 [board draft]). Because of the absence of a dose-response relationship, these data are not adequate for the determination of a cancer effect level. Finally, diethyl phthalate had no tumor initiation or promoting capability in l-year mouse studies (NTP 1993 [board draft]).

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding absorption of diethyl phthalate in humans or animals following inhalation exposure.

2.3.1.2 Oral Exposure

No studies were located regarding the absorption of diethyl phthalate in humans or animals following oral exposure.

2.3.1.3 Dermal Exposure

No *in vivo* studies were located regarding the absorption of diethyl phthalate in humans following dermal exposure. The absorption of diethyl phthalate has been measured *in vitro* through human (from abdominal skin) and rat (from dorsal region) epidermal membranes set up in flow-through diffusion cells (Hotchkiss et al. 1992; Mint et al. 1992; Scott et al. 1987). The extent of percutaneous absorption 72 hours after application to intact, unoccluded human skin was 4.8% of the applied dose (Hotchkiss et al. 1992). Application of diethyl phthalate to the epidermal membranes for 8 hours resulted in a lag phase of absorption followed by a linear phase. Steady-state absorption rates determined for diethyl phthalate for human and rat epidermal membranes showed that diethyl phthalate was absorbed more slowly through human epidermal membranes than through rat epidermal membranes. For humans, the steady-state absorption rate for diethyl phthalate was 1.27 ± 0.11 μg/cm^2/hour. The steady-state absorption rate for rats was 41.37 ± 9.28 μg/cm^2/hour. The human lag time was 6 hours while the lag time for rats was 1 hour. Rat epidermal membrane was more permeable to diethyl phthalate than the human epidermal membrane. The permeability constant of diethyl phthalate for humans was 1.14×10^{-5} cm/hour and for rats it was 37×10^{-5} cm/hour. Dermal application of diethyl phthalate to the human epidermis produced no more skin damage than dermal application of water did. The authors reported that the differences in absorption between the human and rat membranes are to be expected because of the complex differences in the biochemical and structural composition of the two membranes (Scott et al. 1987). These results have been confirmed by additional *in vitro* studies that reported 72-hour absorptions of 36.9% and 5.6% of the applied doses in unoccluded rat and human skin preparations, respectively (Mint et al. 1992).

In rodents, diethyl phthalate is absorbed following dermal exposure. The extent of dermal absorption of diethyl phthalate -was studied using a single dermal application of radiolabeled (^{14}C) diethyl phthalate (5-8 mg/cm^2) to the clipped skin of male rats (Elsisi et al. 1989). The amount of ^{14}C radioactivity excreted was taken as an index of the percutaneous absorption. Twenty-four percent of the dose was excreted in the first 24 hours. The rate of excretion then decreased so that only 11% of the dose was excreted in the next 24 hours. A cumulative total of 50% of the dose was excreted by 7 days, with urinary excretion volumes exceeding fecal volumes (quantitative data not provided).

Seven days after exposure, 34% of the label was in the area of application and 4.8% was in the plastic cap used to protect the application site. Seven other phthalate esters were also tested in the study: dimethyl, dibutyl, dihexyl, di(2-ethylhexyl), diisodecyl, and benzyl butyl phthalates. The results indicated that the length of the side chain affected the dermal uptake of phthalate esters. Skin absorption was inversely proportional to the side chain length-the longer the chain (more than four carbons), the lesser the dermal uptake (Elsisi et al. 1989).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding the distribution of diethyl phthalate in humans or animals following inhalation exposure.

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of diethyl phthalate in humans or animals following oral exposure.

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of diethyl phthalate in humans following dermal exposure.

Results of an experiment in which rats were exposed dermally to a single application of ^{14}C-diethyl phthalate (5-8 mg/cm^2) showed that distribution of the radioactivity is wide but that diethyl phthalate and/or its metabolites are not likely to accumulate to any great extent in tissues (Elsisi et al. 1989). Very little of the ^{14}C radioactivity was found in the tissues 1 week after exposure to diethyl phthalate. The amounts of label found in the brain, lung, liver, spleen, small intestine, kidney, testis, spinal cord, and blood were each less than 0.5% of the administered dose. Adipose tissue, muscle, and skin accounted for 0.03%, 0.14%, and 0.06% of the administered ^{14}C radioactivity, respectively. Thirty-

four percent remained in the area of application, and 4.8% remained in the plastic cap used to protect the application site (Elsisi et al. 1989).

2.3.2.4 Other Routes of Exposure

No studies were located regarding the distribution of diethyl phthalate in humans following exposure by other routes.

^{14}C-diethyl phthalate was administered intraperitoneally (2,800 mg/kg) to pregnant rats on either day 5 or day 10 of gestation (Singh et al. 1975). Results showed that radioactivity from ^{14}C-diethyl phthalate is transmitted across the placenta from mother to fetus for at least 15 days postinjection. ^{14}C radioactivity was widely distributed and was detected (<l%) in maternal blood, placenta, amniotic fluid, and developing fetuses at all gestational stages investigated (Singh et al. 1975).

2.3.3 Metabolism

No *in vivo* studies were located regarding the metabolism of diethyl phthalate in humans or animals. A diagram of the metabolic pathway of diethyl phthalate is not provided since so few data were available. The following elucidation of the metabolism of diethyl phthalate is based on *in vitro* studies, and the studies cited may not represent the *in vivo* situation either qualitatively or quantitatively.

The first step of metabolism involves hydrolysis to a monoester derivative. This was seen in the *in vitro* metabolism of ^{14}C-diethyl phthalate (5-mmol/L solution) by hepatic and small intestine preparations from a rodent (rat), a nonrodent (ferret), and a nonhuman primate (baboon)JLake et al. 1977). Hepatic postmitochondrial supematant and intestinal preparations from the rat, baboon, and ferret were able to catalyze the hydrolysis of diethyl phthalate to its monoester derivative. Enzyme activity was expressed as micromoles of product formed per hour per gram of liver (μmol/hour/g) or per milligram of intestinal mucosal cell protein (μmol/hour/mg). Quantitative species differences were observed in the hepatic and intestinal studies. In the hepatic studies, diethyl phthalate hydrolase

activity decreased in the following order: baboon (516 μmol/hour/g) > rat (231 μmol/hour/g) > ferret (45.9 μmol/hour/g). In the intestinal preparation, diethyl phthalate hydrolase activity decreased in the same order: baboon (4.33 μmol/hour/mg) > rat (0.648 μmol/hour/mg) > ferret (0.053 μmol/hour/mg). Studies were also performed with samples of human duodenum and jejunum tissues. As with the three animal species, human intestinal preparations were also active in the metabolism of diethyl phthalate. The results obtained with human intestinal preparations were expressed as nanomoles of product formed per hour per milligram of intestinal protein (nmol/hour/mg). In the human intestinal preparation, the diethyl phthalate hydrolase activity was 31.2-153 nmol/hour/mg in the duodenum and 129 nmol/hour/mg in the jejunum. Similarly, of the tissues from three rat and one human studied *in vitro,* the rat small intestine hydrolyzed the greatest amount (36.4%) of diethyl phthalate in a 16-hour period (Rowland et al. 1977). These results show a qualitative species similarity in the hydrolytic metabolism of diethyl phthalate in humans, a rodent, a nonrodent, and a nonhuman primate.

In both the Lake et al. (1977) and Rowland et al. (1977) studies, attempts were made to identify the products of hydrolysis. In all instances, only one metabolic product was formed that had matching chromatographic properties in thin-layer chromatographic tests using two different solvent systems. These results showed that diethyl phthalate is mono-de-esterified by the liver and intestines. Since diethyl phthalate was hydrolyzed by rat, baboon, ferret, and human intestinal preparations, the investigators suggested that orally ingested diethyl phthalate would most probably be absorbed from the gut of rats, baboons, ferrets, and humans as the corresponding monoester derivative. Any toxic effects of orally ingested diethyl phthalate would more likely be governed by the properties of the corresponding monoester and/or ethanol rather than by intact diethyl phthalate (Lake et al. 1977). The extent of the hydrolysis of diethyl phthalate under *in vivo* conditions, however, has not been established; consequently, the potential effect of intact diethyl phthalate must also be considered.

Although no data were located specifically regarding the complete *in vivo* metabolism of diethyl phthalate, data concerning alkyl phthalic acid esters in general suggest that the extent of hydrolysis depends on the route of administration. Hydrolysis of other phthalate esters is extensive after oral ingestion, but is also dose-related such that, at higher doses, a greater proportion of the intact diester is absorbed (Albro and Laenhar 1989; Pollack et al. 1985). Furthermore, once formed, the monoester

derivative can be further hydrolyzed *in vivo* to phthalic acid and excreted or conjugated to glucuronide and excreted; the terminal or next-to-last carbon atom in the monoester can be oxidized to an alcohol and excreted; or the alcohol can be successively oxidized to an aldehyde, ketone, or carboxylic acid and excreted (Albro and Moore 1974; Albro et al. 1973; EPA 1989; Kluwe 1982).

In another in vitro study, diethyl phthalate inhibited uridine diphosphate glucuronyl transferase (UDPGT) activity of rat liver microsomal preparations (Gollamudi et al. 1985). UDPGT is an important enzyme involved in the Phase II conjugation and detoxication of many endogenous and xenobiotic substances. After incubation of the microsomes for 3 minutes with a 1.35-mmol/L solution of diethyl phthalate, p-nitrophenol-glucuronyl transferase activity was significantly inhibited (33%). Incubation for 6 minutes resulted in 29% inhibition by a 1.35-mmol/L solution of diethyl phthalate. Diethyl phthalate had no effect on rat liver N-acetyltransferase and microsomal cytochrome P-450 in vitro (Gollamudi et al. 1985).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding the excretion of diethyl phthalate or its metabolites by humans or animals following inhalation exposure.

2.3.4.2 Oral Exposure

No studies were located regarding the excretion of diethyl phthalate or its metabolites by humans or animals following oral exposure.

2.3.4.3 Dermal Exposure

No studies were located regarding the excretion of diethyl phthalate or its metabolites by humans following dermal exposure.

Male rats, exposed to a single dermal application of ^{14}C-diethyl phthalate (5-8 mg/cm^2), excreted 24% of the administered dose in the urine and 1% of the dose in feces within 24 hours (Elsisi et al. 1989). Total recovery of the radiolabel in the urine and feces after 7 days was about 50%. No attempt was made to characterize the metabolites found in the urine (Elsisi et al. 1989).

2.3.4.4 Other Routes of Exposure

No studies were located regarding the excretion of diethyl phthalate or its metabolites by humans following exposure by other routes.

^{14}C-diethyl phthalate (2,800 g/kg) was administered intraperitoneally to pregnant rats on either day 5 or day 10 of gestation (Singh et al. 1975). The results showed that radioactivity in the maternal blood increased, reaching a peak during the first 24 hours. The concentration of radioactivity then diminished quickly. A similar pattern was observed in amniotic fluid and fetal tissues. The reduction in concentration of ^{14}C from these tissues as a function of time was found to fit a first-order excretion curve. From this model curve, the half-life was calculated to be 2.22 days for diethyl phthalate. Although the exact chemical nature of the radioactive compounds was not determined, the investigators reported that some of them were probably mixtures of parent compound, monoester, and phthalic acid (Singh et al. 1975).

2.3.5 Mechanisms of Action

No data regarding the absorption or distribution of diethyl phthalate, after oral or inhalation administration, are available, and the results of dermal studies are inadequate to determine a mechanism of action.

2.4 RELEVANCE TO PUBLIC HEALTH

Populations living in areas surrounding hazardous waste sites may be exposed to diethyl phthalate primarily via ingestion of drinking water. Another possible route of exposure is dermal contact with contaminated water. For the general population (i.e., including individuals not living in the vicinity of

hazardous waste sites), most exposure to diethyl phthalate occurs by the use of consumer products containing it; diethyl phthalate is listed as an ingredient in at least 67 cosmetic formulations at concentrations ranging from ≤0.1% to 50%, although most products contain less than 1% diethyl phthalate. The products may be applied to skin, eyes, hair, and nails, and exposure of the mucous membranes and the respiratory tract can occur. Exposure may be frequent (several times a day) or of prolonged duration (years). Exposure can also occur in people receiving medical treatments that involve the use of polyvinyl chloride tubing from which diethyl phthalate can leach. Exposure of the general population can also occur by ingestion of contaminated foods into which diethyl phthalate has leached from packaging materials, ingestion of contaminated seafood, or drinking contaminated water. Occupational exposure to diethyl phthalate can occur in industrial facilities where diethyl phthalate is used in the manufacture of plastics or consumer products.

The liver may be the only target organ of diethyl phthalate exposure. Very mild hepatic effects are observed only after administration of extremely high doses. Otherwise, the only effects reported in animals after acute- and intermediate-duration oral exposure to this compound were death (acute exposure only), decreases in body weight gain, and organ weight changes that were not accompanied by any biochemical, functional, or histopathological evidence of organ injury. Diethyl phthalate is a mild skin irritant in animals and has been reported to cause minimal ocular irritation. In a twogeneration continuous breeding dietary study in mice, the only effect observed other than a decrease in body weight gain was a reduction in the number of live fetuses born to F, parents. Data on the effects of diethyl phthalate following parenteral administration to experimental animals do not provide any additional indication of the target organs of toxicity for this compound. While skeletal abnormalities (primarily elongated and fused ribs, abnormal or incomplete skull bones, and incomplete or missing tail bones) and increased resorptions were observed following intraperitoneal administration of high doses of diethylphthalate to pregnant rats, no such effects were observed in mice administered the compound orally during gestation. No data are available on the carcinogenicity of diethyl phthalate, and *in vitro* genotoxicity studies gave equivocal, although mostly negative, results.

In vitro studies suggest that diethyl phthalate inhibits mitochondrial respiration in hepatic microsomes by interfering with electron transfer (Haubenstricker et al. 1990; Inouye et al. 1978). While this

finding provides a possible mechanism of action for toxic effects of diethyl phthalate, no functional evidence of mitochondrial impairment have been noted in *in vivo* studies.

Minimal Risk Levels for Diethyl Phthalate

Inhalation

No inhalation MRLs were derived for diethyl phthalate. The only known inhalation study in either humans or animals was conducted in an occupational cohort exposed to vapors from organic solvents and welding fumes of cellulose acetate, which contained 30% diethyl phthalate (Beving et al. 1990). This study was limited because of the small cohort size, co-exposure to other contaminants, inappropriate control data, and little exposure information.

Oral

- An MRL of 7 mg/kg/day has been derived for acute oral exposure to diethyl phthalate. This MRL is based on a reproductive study (Jones et al. 1993) in which rats had Leydig cell ultrastructural changes after receiving 2,000 mg/kg/day diethyl phthalate for 2 days by gavage. This result receives support from findings of decreased testosterone concentrations in diethyl phthalate-treated male rats (Oishi and Hiraga 1980). Furthermore, other investigators (Field et al. 1993) derived a developmental NOAEL of 1,910 mg/kg/day in rats. The acute oral MRL is based on the LOAEL of 2,000 mg/kg/day, divided by an uncertainty factor of 300 (3 for the conversion of a minimal LOAEL to a NOAEL, 10 for interspecies extrapolation, and 10 for the protection of sensitive humans).

- An MRL of 6 mg/kg/day has been derived for intermediate-duration oral exposure to diethyl phthalate. This value is based on a minimal LOAEL of 1,753 mg/kg/day for peroxisomal proliferation, slightly elevated liver weight, and changes in hepatic enzyme activities in male rats (Moody and Reddy 1978). The study receives support from a 13-week mouse dietary study in

which the dose equivalent of 1,625 mg/kg/day was the highest NOAEL for body weight gain deficits (Lamb et al. 1987). The LOAEL was divided by an uncertainty factor of 300 (3 for the conversion of a minimal LOAEL to a NOAEL, 10 for interspecies extrapolation, and 10 for interindividual variation) to arrive at the MRL.

The database was not adequate for determination of a chronic oral MRL for diethyl phthalate.

Death. No studies were located regarding death in humans after exposure to diethyl phthalate. Minimal lethal doses of diethyl phthalate have been estimated for several species of experimental animals following both oral and parenteral administration. These doses range from 1,000 to 4,000 mg/kg (intraperitoneal administration) in rats, rabbits, guinea pigs, and mice and from 4,000 to 5,000 mg/kg (oral administration) in rabbits and guinea pigs (Smyth and Smyth 1931). LD_{50} data were available only for parenteral routes of exposure; the intraperitoneal LD_{50} has been reported to range from 2,830 mg/kg in the mouse (Calley et al. 1966) to 8,324 mg/kg in the rat (Singh et al. 1971, 1972, 1973).

Although available information is insufficient to determine whether exposure to diethyl phthalate in the vicinity of hazardous waste sites could produce death in humans, its widespread use in cosmetic formulations without apparent adverse effects and its virtual lack of toxic effects in animal studies suggest that it is not likely to be associated with death at the levels present in the vicinity of hazardous waste sites.

Systemic Effects

Respiratory Effects. No studies were located regarding respiratory effects in humans or animals following inhalation exposure to diethyl phthalate or in humans following oral or dermal exposure to diethyl phthalate. The results of oral and dermal studies in laboratory animals suggest that the respiratory system is not a target tissue after high dose administration of diethyl phthalate (Brown et al. 1978; NTP 1993 [board draft]).

A transient 71% decrease in respiratory rate was observed in rabbits administered a total intravenous dose of 100 mg/kg diethyl phthalate over a 2-3-minute period (Calley et al. 1966). Respiratory rate returned to baseline within 5 minutes. The mechanism for this effect on respiratory rate is not known. This effect should not be considered relevant to human exposure situations because diethyl phthalate was administered in a bolus intravenous injection, which is not an anticipated human exposure.

Histopathological evaluation revealed no evidence of irritation in the lungs of mice given a single intraperitoneal injection of 2,464 mg/kg diethyl phthalate (Lawrence et al. 1975), or any histopathological changes in the lungs of rodents dermally administered up to 300 μL daily in a chronic study (NTP 1993 [board draft]). No change in lung weight was noted in mice administered 125 mg/kg diethyl phthalate by daily intraperitoneal injection for 6 weeks (Calley et al. 1966). Effects seen after parenteral administration may not be relevant to human exposure.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans or animals following inhalation exposure to diethyl phthalate or in humans following oral or dermal exposure to diethyl phthalate. The results of oral and dermal studies in laboratory animals suggest that the cardiovascular system is not a target tissue after high dose administration of diethyl phthalate (Brown et al. 1978; NTP 1993 [board draft]).

A transient 22% decrease in blood pressure was observed in rabbits administered a total intravenous dose of 100 mg/kg diethyl phthalate over a 2-3-minute period (Calley et al. 1966). Blood pressure gradually returned to baseline levels. The mechanism for this effect on blood pressure is not known. This effect should not be considered relevant to human exposure situations because diethyl phthalate was administered in a bolus intravenous injection, which is not an anticipated human exposure route.

Histopathological evaluation revealed no evidence of treatment-related effects in the hearts of mice given a single intraperitoneal injection of 2,464 mg/kg diethyl phthalate (Lawrence et al. 1975), or any histopathological changes in the hearts of rodents dermally administered up to 300 μL daily in a chronic board draft study (NTP 1993). No change in heart weight was noted in mice administered 125 mg/kg diethyl phthalate by daily intraperitoneal injection for 6 weeks (Calley et al. 1966).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans or animals following inhalation exposure to diethyl phthalate or in humans following oral or dermal exposure to diethyl phthalate. Although high dietary concentrations have been associated with enlarged gastrointestinal organs in rats following oral exposure to diethyl phthalate, these effects are apparently not treatment-related (Brown et al. 1978).

Histopathological evaluation revealed no evidence of irritation in the bowel or pancreas of mice given a single intraperitoneal injection of 2,464 mg/kg diethyl phthalate (Lawrence et al. 1975), or any histopathological changes in the gastrointestinal tracts of rodents dermally administered up to 300 μL daily in a chronic board draft study (NTP 1993).

Hematological Effects. No studies were located regarding hematological effects in humans following inhalation, oral, or dermal exposure to diethyl phthalate.

Limited information available from studies in experimental animals indicates that oral (intermediate-duration), dermal (chronic), or parenteral (single-dose) administration of diethyl phthalate had no effect on any hematological parameters measured (Brown et al. 1978; Lawrence et al. 1975; NTP 1993 [board draft]).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals following inhalation or dermal exposure to diethyl phthalate or in humans following oral exposure to diethyl phthalate. High dietary administration of diethyl phthalate to rats did not affect the histological appearance of skeletal muscle (Brown et al. 1978).

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation, oral, or dermal exposure to diethyl phthalate.

Studies indicate that, while it appears that diethyl phthalate can induce an increase in relative liver weight in experimental animals following oral exposure (Brown et al. 1978; Oishi and Hiraga 1980), the absence of any evidence of treatment-related biochemical, functional, or histopathological changes

in the liver suggests that the increase in liver weight may be an adaptive response rather than a direct toxic effect of diethyl phthalate. Other studies have demonstrated minor changes in liver weight or liver enzyme activity in rats after intermediate-duration oral exposure to diethyl phthalate (Moody and Reddy 1978). Results regarding hepatic peroxisomal proliferation after diethyl phthalate treatment are equivocal (Moody and Reddy 1978; Okita and Okita 1992). No histopathological evidence of hepatic irritation or damage has been found after diethyl phthalate administration in mice and rats (Lawrence et al. 1975; NTP 1993 [board draft]).

Renal Effects. No studies were located regarding renal effects in humans after inhalation, oral, or dermal exposure to diethyl phthalate.

Studies indicate that, while it appears that diethyl phthalate can induce an increase in relative kidney weight in experimental animals following oral exposure (Brown et al. 1978), the absence of any reliable evidence of treatment-related biochemical, functional, or histopathological changes in the kidney suggests that the increase in kidney weight may not be a direct toxic effect of diethyl phthalate.

Endocrine Effects. No studies were located regarding endocrine effects in humans or animals following inhalation or dermal exposure to diethyl phthalate or in humans following oral exposure to diethyl phthalate. Dietary administration of high diethyl phthalate concentrations had no effect on the histopathology of the adrenals, pancreas, thyroid, parathyroid, and/or pituitary of laboratory rodents (Brown et al. 1978).

Dermal Effects. No studies were located regarding dermal effects in humans or animals following inhalation or oral exposure to diethyl phthalate or in humans following dermal exposure to diethyl phthalate.

Diethyl phthalate was shown to be very slightly or slightly irritating when applied repeatedly to the intact or abraded skin, respectively, of an unidentified species (Dow Chemical 1952). In rats treated dermally with diethyl phthalate for 2 years, a mild, apparently adaptive skin acanthosis was found

(NTP 1993 [board draft]). Dermal irritancy from diethyl phthalate should not be a concern near hazardous waste sites.

Ocular Effects. No studies were located regarding ocular effects in humans or animals following inhalation exposure to diethyl phthalate or in humans following oral or dermal exposure to diethyl phthalate. Administration of up to 5% dietary diethyl phthalate had no effect on the histology of the eye (Brown et al. 1978), and ocular irritation tests conducted in rabbits indicate that diethyl phthalate is not a primary ocular irritant (Dear and Jassup 1978; Lawrence et al. 1975).

Body Weight Effects. No studies were located regarding body weight effects in humans or animals following inhalation exposure to diethyl phthalate or in humans following oral or dermal exposure to diethyl phthalate. A variety of data from laboratory animal studies indicates body weight gain decrement at doses far in excess of those expected at hazardous waste sites (Brown et al. 1978; Lamb et al. 1987; NTP 1984, 1993 [board draft]). The available data suggest that the effects are primarily attributable to the stress associated with the dosing level rather than to a direct toxic action.

Although available information is insufficient to determine whether exposure to diethyl phthalate in the vicinity of hazardous waste sites could produce systemic toxicity in humans, its widespread use in cosmetic formulations without apparent adverse effects and its virtual lack of toxic effects in animal studies suggest that it is not likely to be associated with systemic effects at the levels present in the vicinity of hazardous waste sites.

Immunological and Lymphoreticular Effects. A patch test study for allergic contact dermatitis was conducted with workers in a factory that produced shoes from polyvinyl chloride granulate (which contains dioctyl-phthalate) (Vidovic and Kansky 1985). One of 30 workers with dermatitis and 1 of 30 without dermatitis responded positively to diethyl phthalate. None of the controls had a positive response. The authors concluded that these results indicate that the phthalates are sensitizers, and that the positive reaction to diethyl phthalate was most likely due to cross-sensitization with dioctyl phthalate since diethyl phthalate is present in very small amounts in polyvinyl chloride.

Although the available information is insufficient to determine whether exposure to diethyl phthalate at levels present in the vicinity of hazardous waste sites could induce adverse immunological effects in humans, its widespread use in cosmetic formulations without apparent adverse effect suggests that this is not likely.

Neurological Effects. No studies were located regarding neurological effects in humans or animals following inhalation exposure to diethyl phthalate or in humans following oral or dermal exposure. Oral or dermal administration of high doses had no effect on the histopathological appearance of nervous tissue (Brown et al. 1978; NTP 1993).

Acute-duration parenteral administration studies in mice indicate that diethyl phthalate affected pentobarbital-induced sleep (Calley et al. 1966; Lawrence et al. 1975). This effect may be due to a direct action of diethyl phthalate on the central nervous system or an effect on the hepatic enzymes that metabolize pentobarbital. Neither study had been designed to assess the potential neurotoxicity of diethyl phthalate.

Although the available information is insufficient to determine whether exposure to diethyl phthalate at the levels present in the vicinity of hazardous waste sites could induce adverse neurotoxic effects in humans, its widespread use in cosmetic formulations without apparent adverse effect suggests that this is not likely.

Reproductive Effects. No *in vivo* studies were located regarding reproductive effects in humans following exposure to diethyl phthalate. In vitro, diethyl phthalate adversely affected measures of human sperm motility (Fredricsson et al. 1993). The relationship of the exposure concentrations used in this study to expected concentrations resulting from environmental or occupational exposure is unknown.

In a continuous breeding study in CD-l mice, dietary administration of diethyl phthalate produced physiological effects in F_1 parental animals and significantly decreased their litter size (Lamb et al. 1987). No adverse effects on the physiology, fertility, or reproductive performance of the F_0

generation animals were observed. The parental toxicity in the F_1 generation was evident from a significant decrease in body weight, increased prostate weight in males, and increased liver and pituitary weights in females. However, histological findings in the liver and pituitary were not reported, rendering the toxicological significance of a change in these organ weights unknown. Although a significant decrease in sperm concentration occurred in the males, no adverse effect on the fertility was observed. The total number of live pups per litter was significantly lower in the test group compared to the controls.

Several investigators have studied the effects of diethyl phthalate on male reproductive function in rats since other phthalic acid esters have been shown to be toxic to the male reproductive system (ATSDR 1989; Foster et al. 1980, 1983; Gray and Butterworth 1980; Oishi and Hiraga 1980). Testicular and accessory gland weight and histopathology, as well as biochemical parameters of testicular function, were unaffected by the oral administration of diethyl phthalate to male rats at doses up to 1,600 mg/kg/day (Foster et al. 1980, 1983; Gray and Butterworth 1980; Oishi and Hiraga 1980). At 2,000 mg/kg/day, for 2 days, diethyl phthalate produced mitochondrial swelling and smooth endoplasmic reticulum focal dilation and vesiculation in the Leydig cells of rats. These results were not replicated when the primary hydrolysis product, monoethyl phthalate, was tested in Leydig cell culture (Jones et al. 1993). In cultured rat Sertoli cells, diethyl phthalate had no effect on cyclic adenosine monophosphate (AMP) accumulation or basal lactate production (Heindel and Powell 1992).

Although available information is insufficient to determine whether exposure to diethyl phthalate in the vicinity of hazardous waste sites could produce adverse reproductive effects in humans, its widespread use in cosmetic formulations without apparent adverse effects and its virtual lack of toxic effects in animal studies suggest that it is not likely to be associated with reproductive toxicity at levels present in the vicinity of hazardous waste sites.

Developmental Effects. No studies were located regarding developmental effects in humans after exposure to diethyl phthalate.

Maternal rats receiving 3,210 mg/kg/day of diethyl phthalate throughout organogenesis produced offspring with an increased incidence of skeletal variations, particularly supernumerary ribs. This finding was accompanied by decreased weight gain and decreased food and water consumption in the dams. Exposure to this level or lower dietary concentrations resulted in no additional developmental effects (Field et al. 1993). The significance of the increased incidence of skeletal variations is highly questionable because it occurred only at a dietary concentration associated with maternal effects.

After oral administration of diethyl phthalate to mice (4,500 mg/kg/day on gestation days 6-13), there was no significant evidence of maternal toxicity or neonatal developmental effects in a short-term *in vivo* developmental toxicity screen (Hardin et al. 1987). Developmental toxicity did occur in developing rat embryos when the mother was injected intraperitoneally with diethyl phthalate at doses of 2,884, 5,667, or 9,442 mg/kg/day on days 5, 10, and 15 of gestation (Singh et al. 1971, 1972, 1973). Adverse fetal effects included an increase in the number of skeletal abnormalities and resorption sites. No gross (external) malformations or fetal deaths were seen. Fetal weights were significantly reduced ($p<0.01$). The relevance of these findings with regard to potential developmental toxicity in humans exposed to diethyl phthalate in the vicinity of hazardous waste sites is not known; however, the route of exposure used in this animal study is unlikely to occur in humans.

Genotoxic Effects. No *in vivo* studies were located regarding genotoxic effects in humans or animals following exposure to diethyl phthalate. Data from *in vitro* studies using prokaryotic and cultured mammalian cells are presented in Table 2-3.

A comparison of the results of *in vitro* mutagenic assays of diethyl phthalate in various strains of *Salmonella typhimurium* shows contradictory findings. Diethyl phthalate has been shown to be mutagenic for *L typhimurium* strains TA98, TAl00, and TA1535 mostly without metabolic activation (Agarwal et al. 1985; De Marini et al. 1987; Kozumbo et al. 1982). Contrary to these findings, diethyl phthalate has been found to be nonmutagenic in *S. typhimurium* strains TA98, Tal00, TA1535, TA1537, and TA2637 with or without metabolic activation (Agarwal et al. 1985; DeMarini et al. 1987; NTP 1993 [board draft]; Zeiger et al. 1982, 1985).

TABLE 2-3. Genotoxicity of Diethyl Phthalate *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Ames test *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Zeiger et al. 1982, 1985
8-Azaguanine resistance assay *S. typhimurium* (TA100)	Gene mutation	–	+	Seed 1982
Ames test *S. typhimurium* (TA98, TA100)	Gene mutation	–	+	Kozumbo et. al. 1982
Ames test *S. typhimurium* (TA100, TA1535)	Gene mutation	–	+	Agarwal et. al. 1985
(TA98, TA1537, TA2637)	Gene mutation	–	–	
Ames test *S. typhimurium*[1]				
(TA98)	Gene mutation	+	+	De Marini et. al. 1987
(TA100)	Gene mutation	–	–	
Ames test *S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538)	Gene mutation	–	–	Blevins and Taylor 1982
Ames test *S. typhimurium* (TA98, TA100, TA1535, TA1537,	Gene mutation	–	–	NTP 1993
Eukaryotic organisms:				
Mammalian cells:				
Chinese hamster fibroblasts	Chromosomal aberration	–	NA	Ishidate and Odashima 1977
Chinese hamster ovaries	Sister chromatid exchange	+	-	NTP 1993
Chinese hamster ovaries	Chromosomal aberration	-	-	NTP 1993

– = negative result; + = positive result; NA = not applicable to mammalian cell cultures

[1]This test was conducted on a crude solid waste extract.

A well-conducted study investigated the mutagenicity of diethyl phthalate in concentrations ranging from 10 to 10,000 μg/plate in a preincubation modification of the Ames test with and without exogenous metabolic activation using Aroclor 1254-induced rat liver S9 (Zeiger et al. 1982, 1985). The findings indicated that diethyl phthalate was not mutagenic in *S. typhimurium* strains TA1535, TA1537, TA98, or TAl00 with or without metabolic activation. Another Ames test study indicated that diethyl phthalate at 1,000 μg/plate was mutagenic in *S. typhimurium* strain TAl00 but only in the absence of activation (Kozumbo et al. 1982). However, the results are not convincing because the background reversion frequency was too high (291±20) and because the highest response observed for the number of revertants/plate (1.90 ±0.09) was a less than twofold increase. An Ames spot test study indicated that a 50-μg dose of diethyl phthalate did not produce mutagenic results with or without metabolic activation (Blevins and Taylor 1982). The spot test has the limitation of being a qualitative test; a plate incorporation assay should have been conducted before an evaluation of mutagenicity was made. An Ames test study using concentrations of diethyl phthalate ranging from 10 to 2,000 μg/plate showed mutagenicity at 1,500 μg/plate (Agarwal et al. 1985). A threefold increase in the number of revertant colonies was seen in TAl00 without activation, and an approximate twofold increase was seen in TA1535 without activation. An Ames test study examining concentration-response effects in crude wastes and waste extracts containing diethyl phthalate showed a twofold or greater increase in mutagenicity with and without activation in TA98 at a dose (100 μg) much lower than those of other studies suggesting that other impurities may have been present (De Marini et al. 1987). The results of an 8-azaguanine resistance assay in *S. typhimurium* indicated that diethyl phthalate was positive for mutagenicity (Seed 1982). However, the results failed to be significant with less than a twofold increase in the number of mutants per one million cells at the highest concentration of 3.3 mmol/L.

Two chromosomal aberration assays with Chinese hamster fibroblasts and ovaries, respectively, produced negative mutagenic results for diethyl phthalate at concentrations up to 0.324 mg/mL (Ishidate and Odashima 1977; NTP 1993 [board draft]). However, at culture concentrations of 0.05, 0.167, and 0.5 μg/L, diethyl phthalate produced a concentration-related increase in the number of relative sister chromatid exchanges per chromosome. This effect occurred only in the presence of the S9 fraction from rat liver homogenates (NTP 1993 board draft]).

In summary, the results of *in vitro* mutagenicity tests in microbial assays are equivocal. No *in vivo* studies were located. Further studies are required before the genotoxic potential of diethyl phthalate in humans living in the vicinity of diethyl phthalate-contaminated hazardous waste sites can be determined.

Cancer. No studies were located regarding cancer in humans following exposure to diethyl phthalate.

In a recently completed board draft study, dermally applied diethyl phthalate showed no carcinogenic potential in a 2-year rat study and in both initiation and promotion studies in mice. The only evidence for possible carcinogenicity in a 2-year mouse study was an increased incidence of combined hepatic adenomas/carcinomas in both sexes. Growth data suggested that the highest applied dose, 30 μL/day, or 772 mg/kg/day, 5 days/week, was slightly below a maximum tolerated dose (NTP 1993 [board study]). The tumor incidence was dose-related in males only. In general, the results of this study suggest that individuals residing near an NPL site are not at a significant risk of developing cancer from diethyl phthalate exposure.

EPA (IRIS 1994) has classified diethyl phthalate as a Group D chemical--not classifiable as to its carcinogenicity--because pertinent data regarding carcinogenicity were not located in the available literature. Therefore, the carcinogenic potential of diethyl phthalate for humans exposed in the vicinity of hazardous waste sites cannot be determined at this time.

2.5 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).

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 (NAS/NRC 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 biologic 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 diethyl phthalate are discussed in Section 2.5.1.

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 (NAS/NRC 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 often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by diethyl phthalate are discussed in Section 2.5.2.

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, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "Populations That Are Unusually Susceptible."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Diethyl Phthalate

Diethyl phthalate can be detected and quantified in human semen and in animal fat and tissues (Giam and Chan 1976; van Lierop and van Veen 1988; Waliszewski and Szymczymski 1990). Limited data

are available regarding the metabolism of diethyl phthalate. An *in vitro* study revealed that the first step of diethyl phthalate metabolism involves hydrolysis to its monoester derivative, monoethyl phthalate (Lake et al. 1977). However, no data are available regarding the identification of this metabolite in the urine, blood, or tissues. In one study, radiolabeled diethyl phthalate was dermally applied to rats (Elsisi et al. 1989). The radiolabel was recovered in the urine; however, no attempt was made to characterize the metabolites found in the urine. Since the monoester derivative of diethyl phthalate is a probable urinary metabolite (although not identified), it could be a useful biomarker of exposure. There are no other known biomarkers of exposure to diethyl phthalate.

2.5.2 Biomarkers Used to Characterize Effects Caused by Diethyl Phthalate

No biomarkers of effects caused by diethyl phthalate have been identified in humans or animals.

2.6 INTERACTIONS WITH OTHER CHEMICALS

No studies have been identified that investigated the effects of exposure to diethyl phthalate together with other chemicals.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to diethyl phthalate than will most persons exposed to the same level of diethyl phthalate in the environment. Reasons include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, “Populations With Potentially High Exposure.”

Offspring of mice exposed to diethyl phthalate exhibited adverse effects as adults (decreased body weight, increased prostate weight, and decreased sperm count in males; increased liver and pituitary weights in females) (Lamb et al. 1987). These findings suggest that prenatal exposure to diethyl phthalate may be associated with adverse effects in mature offspring. No other information is available on populations with above-average sensitivity to diethyl phthalate.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to diethyl phthalate. 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 diethyl phthalate. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Following dermal exposure to diethyl phthalate, it has been recommended that the skin be immediately washed with copious amounts of soapy water (Stutz and Janusz 1988). If the eyes are exposed to the liquid or vapor, it has been suggested that they be thoroughly flushed with water. Following ingestion of diethyl phthalate, administration of milk, a dilutant and demulcent, has been recommended. Water can be used as an alternative to milk (Haddad and Winchester 1990; Stutz and Janusz 1988). Administration of activated charcoal as an absorptive surface for the contaminant has also been recommended. If ingestion of large amounts of diethyl phthalate has occurred, the administration of a cathartic, such as magnesium sulfate, has been shown to increase the elimination of the substance from the gastrointestinal tract.

2.8.1 Reducing Peak Absorption Following Exposure

Diethyl phthalate is noncorrosive to tissues. Consequently, removal from the gastrointestinal tract either by syrup of Ipecac or by activated charcoal may be possible. These two techniques are effective for approximately 4 to 6-$^{1}/_{2}$ hours after administration, respectively (Ellenhorn and Barceloux 1988). However, because diethyl phthalate has shown little if any toxicological potential, issues regarding reduction in peak absorption may be superfluous.

2.8.2 Reducing Body Burden

Few toxicokinetic data are available on diethyl phthalate. However, even at extremely high exposure concentrations, diethyl phthalate does not have the same toxicological properties as its probable hydrolysis product, ethanol. Because of its apparent negligible toxicity, it is unlikely that body burdens would ever reach levels of concern.

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

Few mechanistic data are available on diethyl phthalate. However, as diethyl phthalate shows little toxicity in human and animal studies, an understanding of events that interfere with the mechanism of action may not be necessary.

2.9 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 dietbyl phthalate 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 diethyl phthalate.

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 or eliminate 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 may be proposed.

2.9.1 Existing Information on Health Effects of Diethyl Phthalate

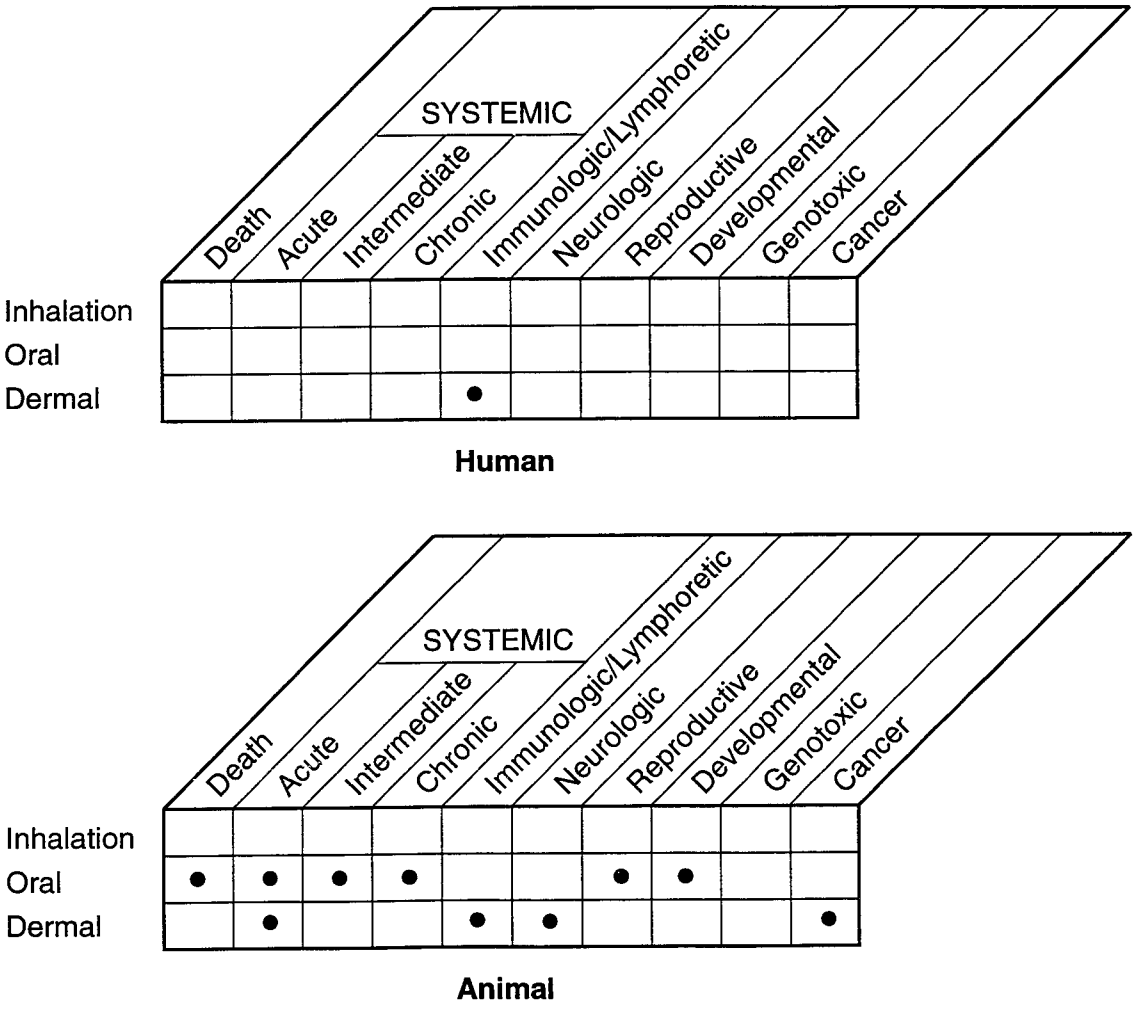
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to diethyl phthalate are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of diethyl phthalate. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs". 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.

As can be seen in Figure 2-2, practically no information is available on the health effects of diethyl phthalate in humans, and very little information is available in animals. Most of the available information on the toxicity of diethyl phthalate in animals comes from studies in which this compound was administered by oral, parenteral (i.e., intraperitoneal, intravenous) or dermal routes. In humans, the only information available is patch test data demonstrating that diethyl phthalate is associated with allergic contact dermatitis in a limited number of polyvinyl chloride workers. Acute oral lethality studies are available in animals. An, acute duration *in vivo* developmental assay and a two-generation reproductive toxicity study were conducted with diethyl phthalate by the oral route. The data avai!able on the effects of dermally administered diethyl phthalate in animals include a board draft report on intermediate duration and chronic exposure studies in rats and mice and additional studies on dermal and ocular irritation.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. There is no information available to identify target organs in humans or animals following acute-duration inhalation or dermal exposure to diethyl phthalate. Although diethyl phthalate has a low vapor pressure ($1.65x10^{-3}$ to $3.45x10^{-4}$ mmHg; Grayson and Fosbraey 1982; Howard et al. 1985) and is relatively nontoxic, airborne vaporization is the major fate process

FIGURE 2-2. Existing Information on Health Effects of Diethyl Phthalate



● Existing Studies

from disposal sites. Consequently, a data need for inhalation studies exists. Minimal lethal oral doses for rabbits and guinea pigs of 4,000-5,000 mg/kg have been reported (Smyth and Smyth 1931), but LD_{50} data are available only for parenteral routes of administration (Galley et al. 1966; Singh et al. 1971, 1972, 1973). A rat study indicated that high dietary levels of diethyl phthalate were associated with ultrastructural testicular changes (Jones et al. 1993). These data were used to calculate an acute-duration oral MRL of 7 mg/kg/day. There are insufficient pharmacokinetic data available to support the extrapolation of results obtained after oral administration to other routes of exposure. However, given findings of minimal toxicity at high oral or dermal doses administered for periods greater than 14 days, additional acute-duration exposure studies seem unnecessary.

Intermediate-Duration Exposure. The only effects seen after a 16-week dietary administration study with diethyl phthalate in rats were a decrease in body weight gain with a concomitant decrease in food consumption (Brown et al. 1978). In 4-week dermal studies with rats and mice, diethyl phthalate produced no observable histopathological changes on any tissue (NTP 1993 [board draft]). Experimental studies (Moody and Reddy 1978; Okita and Okita 1992) indicate that high diethyl phthalate doses have only slight effects on peroxisomal proliferation and have a minor effect on microsomal enzyme induction. The Moody and Reddy (1978) data were used to support an intermediate-duration MRL of 6 mg/kg/day. An inhalation toxicity study would help determine route-specific effects via the potentially most significant exposure route.

Chronic-Duration Exposure and Cancer. No chronic or carcinogenicity studies have been conducted in humans or animals exposed orally or by inhalation. The results of a chronic-duration dermal application study and initiation-promotion experiments indicate that diethyl phthalate has little if any nonneoplastic or neoplastic potential at doses near a Maximum Tolerated Dose (NTP 1993 [board draft]). Although chronic oral data are lacking, the results from the complete database suggest that lifetime exposure near NPL hazardous waste sites would not result in a significant health hazard. A long-term inhalation study to address this issue, in a representative animal species, would help to validate this conclusion.

Genotoxicity. No *in vivo* studies were located regarding genotoxic effects in humans or animals following inhalation, oral, or dermal exposure to diethyl phthalate. The results of in *vitro* mutagenicity tests in microbial systems are equivocal (Agarwal et al. 1985; DeMarini et al. 1987; Kozumbo et al. 1982; NTP 1993 [board draft]; Zeiger et al. 1982, 1985). These studies indicate negative findings for chromosomal aberrations in mammalian cultures, increased sister chromatid exchange frequencies in mammalian cultures, and generally negative incidences of reverse mutation in prokaryotic assays. Given the inconsistent nature of the *in vitro* results, *in vivo* tests of chromosome aberrations in animals exposed to diethyl phthalate would be useful to elucidate the genotoxic potential of this compound.

Reproductive Toxicity. There is no information on the reproductive effects of diethyl phthalate in humans following inhalation, oral, or dermal exposure. This result is consistent with reproductive data from other straight chain-substituted phthalate esters. Diethyl phthalate may produce minor adverse effects on male reproductive organ function or morphology in experimental animals (Jones et al. 1993). In a two-generation continuous breeding dietary reproductive toxicity study in mice, no adverse effect on any measured parameter of fertility was observed in either generation; however, the total number of live pups per litter was significantly lower in litters born to F, parents (Lamb et al. 1987). Oral administration of diethyl phthalate at 2 g/kg body weight in rats resulted in ultrastructural Leydig cell changes, including mitochondrial swelling with focal dilatation of the smooth endoplasmic reticulum (Jones et al. 1993). In the same study, however, *in vitro* Leydig cell testosterone secretion was unaffected by 1 millimolar (mM) monoethyl phthalate treatment. At 0.33 mM and above, diethyl phthalate adversely affected sperm motility (Fredricsson et al. 1993). Monoethyl phthalate at 0.1 mM had no effect on *in vitro* Sertoli cell function (Heindel and Powell 1992). These data confirm and extend the results of previous studies indicating that testicular functional and anatomical changes inconsistently occur at high diethyl phthalate exposure levels. Although few results on female reproductive effects are available, an analysis of the data from both reproductive and developmental studies suggest that no adverse reproductive effects would occur at exposure levels expected near NPL sites. Consequently, no data needs currently exist.

Developmental Toxicity. No information is available on the developmental effects of diethyl phthalate in humans following inhalation, oral, or dermal exposure. No developmental effects were noted in an acute-duration oral *in vivo* developmental toxicity screen in mice (Hardin et al. 1987). An increased incidence of skeletal variations in rat pups, at an oral diethyl phthalate dose of 3,210 mg/kg/day, may have been associated with either a direct toxic effect or with transient maternal malnutrition (Field et al. 1993). However, skeletal abnormalities and an increased number of resorptions were noted following intraperitoneal administration of 3,000-9,000 mg/kg/day diethyl phthalate to pregnant rats (Singh et al. 1971, 1972, 1973). Because of the administration route and the high dose administered, the relevance of this study to human exposure is not known. In general, the data from oral studies, using extremely high exposure conditions, indicate that diethyl phthalate would not be a developmental hazard at occupational or environmental concentrations. Consequently, no data needs currently exist.

Immunotoxicity. Diethyl phthalate may be a contact sensitizer in a limited number of human receptors (Greif 1967; Oliwiecki et al. 1991; Vidovic and Kansky 1985). However, the possibility of cross-sensitization with other compounds, including other phthalate esters, renders the significance of these findings questionable. No reliable animal data were available. A more comprehensive dose-response study using well established sensitized and nonsensitized animal models may help clarify the potential of diethyl phthalate as an immunotoxic agent.

Neurotoxicity. No information is available on the neurological effects of diethyl phthalate in humans or animals following inhalation, oral, or dermal exposure. Acute-duration parenteral administration studies in mice indicate that diethyl phthalate affected pentobarbital-induced sleep (Calley et al. 1966; Lawrence et al. 1975). However, this effect may be due to a direct action of diethyl phthalate on. the central nervous system or an effect on the hepatic enzymes that-metabolize pentobarbital. There currently exists a need for observing overt or histopathological evidence of neurological aberrations in a controlled animal study.

Epidemiological and Human Dosimetry Studies. No epidemiological studies are available on populations that have been exposed solely to diethyl phthalate. As a result of its use, together with other phthalate esters, as a plasticizer for cellulose ester films and in extruded materials and a variety of consumer products (including cosmetics and skin care preparations) (Anonymous 1985; Kamrin and Mayor 1991), exposure of the general population and of workers in occupational settings is significant. Therefore, it is unlikely that both a specific subpopulation exposed only to diethyl phthalate and a control population with no known exposure could be identified. Given this inability to find suitably exposed subpopulations, as well as diethyl phthalate's low systemic toxicity and apparent lack of target organ effects at occupational or environmental concentrations, epidemiological and human dosimetry studies are both unfeasible and unnecessary. A better understanding of the role of the liver as a potential target organ should take precedence.

Biomarkers of Exposure and Effect. Ethanol and phthalic acid, the putative diethyl phthalate hydrolysis products, are nonspecific biomarkers. The pharmacokinetics of the only potential specific biomarker of exposure, monoethyl phthalate, are unknown. Furthermore, no adverse effects specific to diethyl phthalate have been identified. Because of the unlikelihood that the vast proportion of individuals occupationally or environmentally exposed to diethyl phthalate will show any adverse effects, research to find biomarkers of exposure seems unnecessary.

Since exposure to diethyl phthalate does not produce a unique clinical disease state, no biomarkers of effect have been identified.

Absorption, Distribution, Metabolism, and Excretion. No studies were located regarding the absorption of diethyl phthalate following inhalation or oral exposure in humans or animals. No *in vivo* studies were located regarding absorption of diethyl phthalate following dermal exposure-in humans. However, an *in vivo* animal study (Elsisi et al. 1989) and several *in vitro* studies (Hotchkiss et al. 1992; Mint et al. 1992; Scott et al. 1987) indicate that diethyl phthalate is absorbed through the skin of humans and rats. Using the amount of radiolabel present as an index of percutaneous absorption, 24% of a single dose of 34.89 mg/kg applied dermally to rats was excreted in the first 24 hours (Elsisi et al. 1989). A cumulative total of 50% was excreted after 7 days. An in vitro study of the absorption of

diethyl phthalate through human and rat epidermal membranes indicates that diethyl phthalate is slowly absorbed through both human and rat skin; however, diethyl phthalate was absorbed more quickly through rat skin than through human skin. The results showed that rat skin was more permeable to diethyl phthalate than human skin. Following contact with diethyl phthalate, there was an increase in the permeability for both human and rat skin. However, rat skin showed a much greater change in permeability indicating that irreversible alteration of the membrane permeability occurred as a result of exposure to diethyl phthalate (Scott et al. 1987). Additional oral and inhalation *in vivo* absorption data would be useful in order to assess the relative rates and extent of absorption and may help in the identification of potential mechanisms of action.

No studies were located regarding the distribution of diethyl phthalate following inhalation or oral exposure in humans or animals. No studies were located regarding distribution in humans following dermal exposure. Only one study was located regarding distribution in animals following dermal exposure (Elsisi et al. 1989). The results of this acute study in rats showed that although tissue distribution was wide, diethyl phthalate and/or its metabolites are not likely to accumulate in the tissues to any great extent. Less than 5% of the administered dose was found in the tissues (brain, lung, liver, spleen, small intestine, kidney, testis, spinal cord, blood, adipose tissue, muscle, and skin). An acute intraperitoneal study in rats showed that diethyl phthalate crossed the placenta from mother to fetus and was distributed in maternal blood, placenta, amniotic fluid, and fetal tissue; however, very little (<1%) of the dose was present (Singh et al. 1975). Limited additional experimental data for both humans and animals would be useful in order to adequately assess similarities and differences in the distribution of diethyl phthalate and/or its metabolites after oral or inhalation exposure.

Very limited information is available regarding the metabolism of diethyl phthalate (Gollamudi et al. 1985; Lake et al. 1977). In vitro studies indicate that the first step in the metabolism of diethyl phthalate involves hydrolysis to a monoester derivative (Lake et al. 1977). Although data on the metabolism of phthalate diesters as a class were located, more specific data on diethyl phthalate would help to adequately characterize the metabolism of this compound. The significance of high dose effects observed in toxicity studies may be clarified by metabolism findings. For example, properly designed studies would indicate whether metabolic saturation occurs at high doses, which may help

explain the excess metabolic demands that such doses entail. This information may be essential for determining whether an MRL can be derived.

No studies were located for humans or animals regarding the excretion of diethyl phthalate following inhalation or oral exposure. Very limited data indicate that diethyl phthalate is excreted primarily in the urine following acute dermal exposure in rats (Elsisi et al. 1989). An excretion half-life of 2.2 days was calculated for diethyl phthalate in rats (Singh et al. 1975). Dose-response information on the identity of the metabolites excreted would help clarify the significance of high-dose effects, including hepatic peroxisomal proliferation (Moody and Reddy 1978), ultrastructural testicular changes (Jones et al. 1993), and body weight gain inhibition (Lamb et al. 1987).

Comparative Toxicokinetics. Limited in vitro data indicate that both humans and rats absorb diethyl phthalate relatively slowly through the skin but that rats seem to absorb the compound more quickly than humans (Elsisi et al. 1989; Scott et al. 1987). Few data are available to adequately indicate the similarities and/or differences in target organs. Toxicokinetic studies (in vitro) have been performed in both humans and animals (multiple species); however, the data are extremely limited. Humans and animals (rodent, nonrodent, and nonhuman primate) were qualitatively similar in their ability to hydrolyze diethyl phthalate in the intestines and liver. However, quantitative species differences were observed in the rates of hydrolase activity of the rodent, nonrodent, and nonhuman primate with the order being primate > rodent > nonrodent (Lake et al. 1977). Excretion data identifying the metabolites of diethyl phthalate found in the urine and feces of humans and in multiple animal species would be useful in order to adequately assess which animals can serve as the best models.

Methods for Reducing Toxic Effects. All of the treatment methods currently available for use in diethyl phthalate ingestion or skin contact are supportive in nature and/or involve decreasing absorption or hastening elimination of diethyl phthalate (Haddad and Winchester 1990; Stutz and Janusz 1988). Since the mechanism of diethyl phthalate toxicity is not known, there are currently no methods geared towards mitigating the effects of diethyl phthalate by interfering with its mode of action. Therefore, more information on the mechanism of action for diethyl phthalate would be useful

in order to devise methods for the mitigation of any potential toxic effect, such as peroxisomal proliferation.

2.9.3 On-going Studies

No on-going studies on the health effects or toxicokinetics of diethyl phthalate were found.

3. CHEMICAL AND PHYSICAL INFORMATION

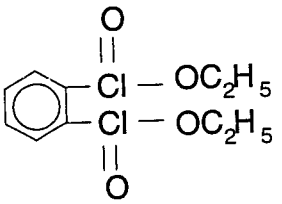
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of diethyl phthalate is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of diethyl phthalate is located in Table 3-2.

TABLE 3-1. Chemical Identity of Diethyl Phthalate

Characteristic	Information	Reference
Chemical name	Diethyl phthalate	HSDB 1994
Synonym(s)	1,2-Benzenedicarboxylic acid diethyl ester; diethyl *o*-phthalate; ethyl phthalate; *o*-benzenedicarboxylic acid diethyl ester; diethyl ester phthalic acid; phthalol; DEP; diethyl-*o*-phenylenediacetate	EPA 1989; HSDB 1994; OHM/TADS 1991
Registered trade name(s)	Neantine; Palatinol A; Phthalol; Placidol E; Solvanol; Unimoll DA; Anozol; Estol 1550	HSDB 1994
Chemical formula	$C_{12}H_{14}O_4$	HSDB 1994
Chemical structure		
Identification numbers:		
CAS registry	84-66-2	HSDB 1994
NIOSH RTECS	TI1050000	HSDB 1994
EPA hazardous waste	UO88	HSDB 1994
OHM/TADS	7217236	HSDB 1994
DOT/UN/NA/IMCO shipping	No data	
HSDB	926	HSDB 1994
NCI	NCI-C60048	HSDB-1994

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

TABLE 3-2. Physical and Chemical Properties of Diethyl Phthalate (*continued*)

Characteristic	Information	Reference
Henry's law constant[a]	7.8×10^{-7} atm m^3/mol	EPA 1989
Autoignition temperature	457°C	HSDB 1994
Flashpoint	161°C	HSDB 1994
Flammability limits[b]	0.7% at 187°C	HSDB 1994
Conversion factors	9.07 mg/m^3 = 1 ppm	HSDB 1994
Explosive limits	No data	

[a]Temperature not specified
[b]Lower flammability limit given; upper limit not available

TABLE 3-2. Physical and Chemical Properties of Diethyl Phthalate

Characteristic	Information	Reference
Molecular weight	222.23	Anonymous 1988; Autian 1973
Color	Colorless	HSDB 1994
Physical state	Liquid	HSDB 1994
Melting point	-40.5°C	HSDB 1994
Boiling point	295-302°C	Autian 1973; Banerjee et al. 1990; EPA 1989; HSDB 1990; OHM/TADS 1991; Sax and Lewis 1989
Density		
at 25°C	1.120 g/mL	Anonymous 1985
Odor	Slight aromatic odor	HSDB 1994
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 25°C	1,080 mg/L	Howard et al. 1985; HSDB 1994
Organic solvent(s)	Alcohol, ether, acetone, and benzene; vegetable oils; ketones, esters, aromatic hydrocarbons, and aliphatic solvents	HSDB 1994
Partition coefficients:		
Log K_{ow}	1.4–3.3	Callahan et al. 1979; Howard et al. 1985: HSDB 1994; Laane et al. 1987; Leyder and Boulanger 1983; Veith et al. 1980
Log K_{oc}	2.65	Wolfe et al. 1980b
Vapor pressure:		
at 20°C	3.45×10^{-4} mmHg	Grayson and Fosbraey 1982
at 25°C	1.65×10^{-3} mmHg	Howard et al. 1985; HSDB 1994

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Diethyl phthalate is produced industrially by the reaction of phthalic anhydride with ethanol in the presence of concentrated sulfuric acid catalyst (Anonymous 1985; HSDB 1994). Phthalic anhydride is produced by either the oxo process or the Ald-Ox process from ethanol and the oxidation of naphthalene or o-xylene (Peakall 1975). The purity of manufactured phthalate esters is reportedly between 99.70% and 99.97% with the main impurities being isophthalic acid, terephthalic acid, and maleic anhydride (Peakall 1975). The U.S. production volume of diethyl phthalate gradually declined from approximately 21 million pounds in 1980 to 19 million pounds in 1987 (USITC 1981, 1988). Production volumes increased again in 1988 to 26 million pounds (Kamrin and Mayor 1991). Currently the four U.S. facilities that reportedly produce diethyl phthalate are Eastman Chemical Company (Kingsport, Tennessee), Reilly Industries, Inc. (Greensboro, North Carolina), BASF Corporation (Parsippany, New Jersey), and Huls America, Inc. (Piscataway, New Jersey) (HSDB 1994; SRI 1991). Since diethyl phthalate releases are not required to be reported under the Super-fund Amendments and Reauthorization Act (SARA) Section 313, there are no data on diethyl phthalate in the Toxics Release Inventory (TR188 1991, 1993).

4.2 IMPORT/EXPORT

U.S. imports of diethyl phthalate decreased from 610,684 pounds in 1978 to 511,475 pounds in 1982 (HSDB 1994). More recent data on imports are not available. There are no data available on U.S. exports of diethyl phthalate.

4.3 USE

There is a wide variety of consumer products that contain diethyl phthalate or are covered with diethyl phthalate-containing plastic packaging (Kamrin and Mayor 1991). Diethyl phthalate is used as a plasticizer for cellulose ester plastic films and sheets (photographic, blister packaging, and tape applications) and molded and extruded articles (consumer articles such as toothbrushes, automotive components, tool handles, and toys). Diethyl phthalate was reported as an ingredient in 67 cosmetic formulations at concentrations ranging from ≤0.1 % to 25-50%. These cosmetics included bath preparations (oils, tablets, and salts), eye shadows, toilet waters, perfumes and other fragrance preparations, hair sprays, wave sets, nail polish and enamel removers, nail extenders, nail polish, bath soaps, detergents, aftershave lotions, and skin care preparations (Anonymous 1985; Kamrin and Mayor 1991). More specifically, diethyl phthalate is used in nail polish as a solvent for nitrocellulose and cellulose acetate, in perfumes as a fixative and solvent, in toilet preparations as an alcohol denaturant, and in fingernail elongators as a plasticizer (Anonymous 1985; EPA 1989; Hawley 1987; Verschueren 1983). In addition, diethyl phthalate is used as a component in insecticide sprays and mosquito repellents, as a camphor substitute, as a plasticizer in solid rocket propellants, as a wetting agent, as a dye application agent, as an ingredient in aspirin coatings, as a diluent in polysulfide dental impression materials, and in adhesives, plasticizers, and surface lubricants used in food and pharmaceutical packaging (Anonymous 1985; EPA 1989; Guy and Powers 1977; Hawley 1987; Verschueren 1983).

4.4 DISPOSAL

Recommended methods for disposal of diethyl phthalate include incineration and landfill. The best techniques for incineration are liquid injection and rotary kiln. The incineration range for the former is 650°C to 1,600ºC, with a residence time of 0.1 to 2 seconds. The temperature range for rotary kiln incineration is 820°C to 1,600ºC. Fluidized bed incineration, with a temperature range of 450°C to 980°C is also a good technique (HSDB 1994). Combustion of diethyl phthalate may be improved by mixing with a more flammable solvent (OHM/TADS 1991). Landfill may be implemented after adsorption on vermiculite or a similar adsorbent. Before implementing land disposal of waste residue, environmental regulatory agencies should be consulted for guidance on acceptable disposable practices (HSDB 1994).

5. POTENTIAL FOR HUMAN EXPOSURE

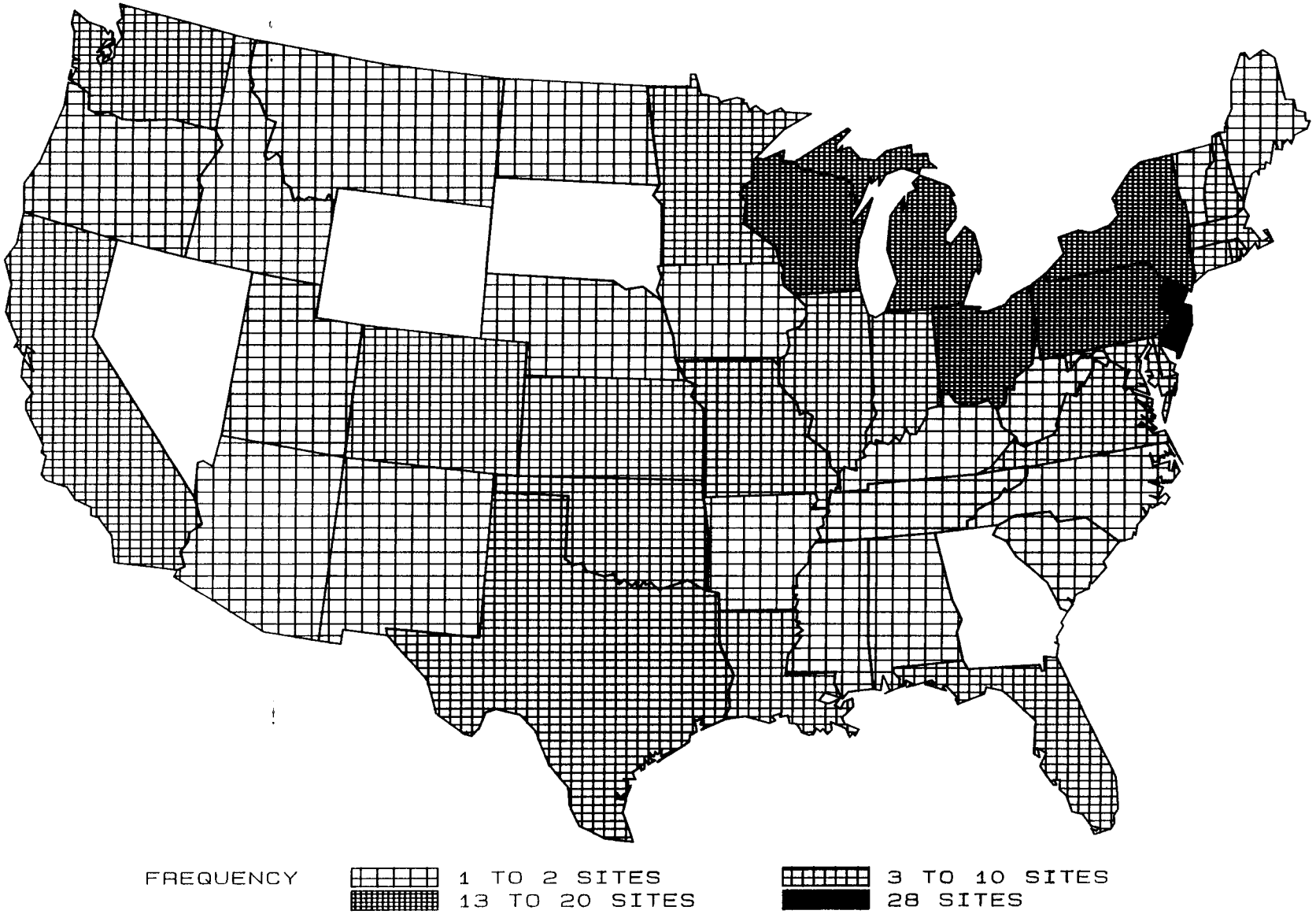
5.1 OVERVIEW

As a result of its use as a plasticizer for cellulose ester films and extruded materials and in a variety of consumer products, human exposure to diethyl phthalate is expected to be significant. Diethyl phthalate may be released to the environment as a result of manufacturing processes, disposal in landfills, incomplete incineration, or by leaching or volatilization from products in which it is used. Releases are expected to be primarily to water or to soil as a result of leaching from landfills. Diethyl phthalate may enter the atmosphere through combustion of plastics and, to a lesser degree, by volatilization. Diethyl phthalate partitions to particulate matter in water or sediments, where it can be biodegraded either aerobically or anaerobically; other degradation processes are not significant. From soils with low organic matter content, diethyl phthalate may enter the underlying groundwater. Diethyl phthalate may bioaccumulate to some degree in aquatic organisms, but it is unlikely to biomagnify up the food chain. Diethyl phthalate has been identified in 248 of the 1,397 NPL hazardous waste sites (HAZDAT 1994). The frequency of these sites within the Unites States can be seen in Figure 5-l. Of these sites, 241 are located in the United States, and 1 is located in Guam (not shown).

Diethyl phthalate is likely to undergo biodegradation in the environment. Abiotic degradation processes such as hydrolysis, oxidation, and photolysis are unlikely to play significant roles in the environmental fate of diethyl phthalate.

Diethyl phthalate-has-been detected in ambient indoor air, waste waters from industrial facilities, surface waters and sediments, and marine waters. Fish and other aquatic biota living in contaminated waters have been shown to contain diethyl phthalate in their tissues, although depuration is relatively rapid when the organisms are placed in uncontaminated water.

FIGURE 5-1. FREQUENCY OF NPL SITES WITH DIETHYL PHTHALATE CONTAMINATION *



*Derived from HazDat 1994

Human exposure to diethyl phthalate can result from breathing contaminated air, eating foods into which diethyl phthalate has leached from packaging materials, eating contaminated seafood, drinking contaminated water, or as a result of medical treatment involving the use of polyvinyl chloride tubing (e.g., dialysis patients). The use of diethyl phthalate in consumer products, however, is likely to be the primary source of human exposure. Diethyl phthalate has been detected in adipose tissue samples taken from people (including children) nationwide. Occupational exposure may occur in industrial facilities where diethyl phthalate is used in the manufacture of plastics or consumer products.

Diethyl phthalate is not included on the Toxics Release Inventory as a reportable chemical.

Releases to the environment occur primarily as a result of production and manufacturing of diethyl phthalate itself and also during use and disposal of products containing diethyl phthalate. Minor releases occur as a result of biosynthesis (Pierce et al. 1980). It has been estimated that 7,600 metric tons of diethyl phthalate are released annually to the environment (EPA 1981b).

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Approximately 75% of the total environmental release of phthalate plasticizers from dump sites result from low-temperature burning, with subsequent vaporization. Diethyl phthalate may also be released directly to the atmosphere as a result of volatilization/evaporation from consumer items such as cosmetics and toiletries, insect repellents, and insecticides (Peakall 1975).

Based on 1977 production data, EPA (1981a) estimated that 200 metric tons of diethyl phthalate would be released annually to the air as a result of manufacturing, use, or disposal, and another 200 metric tons would be released annually as a result of incineration of diethyl phthalate materials.

5.2.2 Water

Diethyl phthalate was detected in 4.96% of the groundwater samples and 1.42% of the surface water samples taken at NPL sites included in the Contract Laboratories Program Statistical Database (CLPSD) at mean concentrations of 12.50 and 12.10 µg/L, respectively, in the positive samples (CLPSD 1989). Note that the information used from the CLPSD includes data from NPL sites only.

It has been estimated that the phthalate esters released to the environment may be approximately 1% of the phthalate content of plastic materials in direct contact with water or other liquids (Peakall 1975).

EPA (1981b) estimated that 300 metric tons of diethyl phthalate would be released annually to surface water as a result of manufacturing, use, or disposal, based on 1977 production data.

5.2.3 Soil

Based on 1977 production data, EPA (1981b) estimated that 6,800 metric tons of diethyl phthalate would be released annually to the environment as a result of landfilling activities.

Diethyl phthalate has been detected in 4.26% of the soil samples taken from the NPL sites included in the CLPSD at a mean concentration of 39.06 µg/kg in the positive samples (CLPSD 1989). Note that the information used from the CLPSD includes data from NPL sites only.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Based on a log octanol water partition coefficient (K_{ow}) ranging from 1.40 (measured, 2.67 estimated; Veith et al. 1980) to 3.3 (Laane et al. 1987), diethyl phthalate is considered to be lipophilic and consequently may be taken up by lipids in aquatic organisms. However, diethyl phthalate may also be degraded by these organisms suggesting that it is unlikely to biomagnify up the food chain (EPA

1979). The bioconcentration factor (BCF) for diethyl phthalate using the bluegill sunfish (Lepomis macrochirus) in a 21-day study was 117 (log BCF = 2.07; mean water concentration of diethyl phthalate = 9.42 µg/L), and the half-life in fish tissue was between 1 and 2 days (Barrows et al. 1980; Veith et al. 1980). A study of the uptake of diethyl phthalate through the gills of English sole (Purophrys vetulus) indicated that the uptake efficiency was inversely correlated with weight-specific ventilation volume and was not correlated with fish weight or with diethyl phthalate exposure concentration; the mean uptake was only 11.3% (Boese 1984).

Air

No studies were located on the transport and partitioning of diethyl phthalate in the atmosphere. Volatilization of diethyl phthalate is expected to be slow based on its low vapor pressure of 1.65×10^{-3} mmHg at 25°C (Howard et al. 1985). Diethyl phthalate may be removed from the atmosphere by wet or dry deposition (EPA 1989).

Water

A computer simulation of the transport of diethyl phthalate in four aquatic systems using the Exposure Analysis Modeling System (EXAMS) estimated that, based on a sediment/water partition coefficient (K_{oc}) of 4.5×10^{2}, >90% of the diethyl phthalate would be distributed to the water column in a river, eutrophic lake, or oligotrophic lake ecosystem, with less than 10% found in bottom sediments. In a pond, 70% of diethyl phthalate would be in the water column with 30% found in the bottom sediment (Wolfe et al. 1980a).

Major transport-mechanisms for diethyl phthalate include sorption onto suspended particulates and biota and possibly the formation of complexes with humic substances in the water (EPA 1979). Based on a Henry's law constant of 7.8×10^{-7} atm m^3/mol, volatilization from water is not expected to be a significant removal process for diethyl phthalate (EPA 1989).

5. POTENTIAL FOR HUMAN EXPOSURE

Studies of phthalate esters in surface sediment samples of the River Mersey in England (Preston and Al-Omran 1989) showed that, in one sample, diethyl phthalate was enriched in the coarser sediment fractions with high lipid content (0.102 µg/g dry weight, background 0.050 µg/g); however, in another sample, diethyl phthalate was more concentrated in the finer particle fraction (0.060 µg/g, background 0.013 µg/g). The greater presence of diethyl phthalate in the sediment with high lipid content suggests that hydrophobic adsorption can occur, although possible mechanisms were not discussed. A study of the presence of diethyl phthalate in waste water and sediments from Canadian coal mines found that diethyl phthalate added to distilled water over mine sediment would remain in the water column rather than partition onto the sediment (Atwater et al. 1990).

Diethyl phthalate adsorbs to suspended particles in marine waters, with the maximum adsorption occurring onto particles of 353-698 µm in size (Al-Omran and Preston 1987).

Soil

Diethyl phthalate is fairly mobile in soil, based on tests of the absorption of diethyl phthalate from double-distilled water onto composite soil (1.59% organic carbon); diethyl phthalate moved through the soil at half the rate of water (Russell and McDuffie 1987). In undisturbed soil columns, phthalate ester transport was determined by both physical and chemical nonequilibrium processes (Zurmuhl et al. 1991). In general, the chemical disequilibrium was greater in a soil with greater organic carbon content than in a low organic carbon-content soil. The investigators attributed this finding to the greater sorption capacity of the former soil type. The mobility of diethyl phthalate through the soil columns was greater than the mobility of the more lipophilic dibutyl, butyl benzyl, and di(2-ethylhexyl) phthalate esters.

The presence of diethyl phthalate in groundwater in Phoenix, Arizona, was studied using a rapid infiltration system. Diethyl phthalate, present in the sewage infiltrate at 0.231 µg/L, was reduced to 0.017 µg/L or less (detected but too low to be quantified) in groundwater samples taken from a 60-foot well depth (Tomson et al. 1981). Further studies with this system showed that infiltrate basin water containing initial concentrations of diethyl phthalate of 10-20 µg/L decreased by 75-95% after infiltration. Removal was greatest in water taken from deeper sampling wells (30 versus 18 feet). The

ultimate rate of removal was independent of whether the basin water had been chlorinated or not. However, chlorination appeared to speed the removal of diethyl phthalate in the shallow well (Bouwer et al. 1984). The removal of diethyl phthalate from waste waters using soil as a sorption medium was not confirmed by Hutchins et al. (1983), who found that treatment of secondary effluents containing diethyl phthalate at 0.19 µg/L by a rapid infiltration system in Fort Polk, Louisiana, resulted in the presence of diethyl phthalate in the associated groundwater at 0.26 µg/L. It was suggested that this may, in part, be due to the low concentration of diethyl phthalate, which underutilized the biodegradation capacity of the soil column. The removal of diethyl phthalate from waste water by absorption or biodegradation in the soil is dependent on the soil type and, in some cases, on its ability to be transported through soils to underlying groundwaters.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Ultraviolet absorption spectra for diethyl phthalate suggest that, although there is a potential for photodegradation in the atmosphere, this is not a significant removal process (EPA 1989). Diethyl phthalate may exist in the atmosphere in vapor form and adsorb to airborne particulates. Diethyl phthalate reacts photochemically with hjrdroxyl radicals in the air with an estimated half-life of 22.2 hours (HSDB 1994).

5.3.2.2 Water

The use of a computer-simulated model for aquatic ecosystems (EXAMS) indicated that, compared with biodegradation, .abiotic hydrolysis and photolysis are minor degradation processes for diethyl phthalate in most aquatic ecosystems. Only in an oligotrophic lake was photolysis a more significant degradation process than biodegradation for diethyl phthalate. In a river system with a detention time of 1 hour, diethyl phthalate would be virtually unchanged and would be lost only by export (Wolfe et al. 1980a). The hydrolysis half-life for diethyl phthalate in water at pH 7.0 and 30°C is estimated to be greater than 18 years (EPA 1979). The oxidative half-life for alkyl phthalates is estimated to exceed 3 years (EPA 1989). Lewis et al. (1984b) studied the degradation of diethyl phthalate in a

simulated aquatic ecosystem consisting of microbial growth attached to submerged surfaces or suspended as mats or streamers in the water (*aufwuchs*). Diethyl phthalate did not adsorb to any aquatic surfaces (including autoclaved *aufwuchs*, sediment, and equipment surfaces). It was virtually untransformed by photolysis (<l%), and only 10 µg/L of 191 µg/L diethyl phthalate was lost by hydrolysis in 12 hours at a pH of 10. Degradation occurred as a result of bacterial transformation (95-99% of loss), which was dependent on the surface area colonized by the bacteria and unaffected by dissolved organic carbon, nitrogen, and phosphorus. However, as bacterial densities increased in the aufwuchs, the rate of transformation decreased, possibly as a result of the increased growth of bacteria that were unable to degrade diethyl phthalate (Lewis and Holm 1981). Further studies using laboratory microcosms and field-collected microbiota found that while diethyl phthalate was degraded in all of the laboratory studies, degradation occurred at only 2 of 10 field sites. The degradation rates were similar, however, for both ecosystems (Lewis et al. 1985). Diethyl phthalate was degraded in 3 hours by *Brevibacterium sp.* isolated from several lakes and rivers in Georgia. The rate of degradation was increased by the addition of spent fungal culture medium to the bacterial culture (Lewis et al. 1984a).

A phthalate ester-hydrolyzing enzyme purified from *Nocardia erythropolis,* a bacterium found in soils and waste waters, had relative enzyme activity using diethyl phthalate of 76.3% (relative to 100% enzyme activity for di-[2-ethylhexyl] phthalate). Diethyl phthalate was hydrolyzed to the free phthalic acid and alcohol. The phthalic acid would be metabolized by intradiol fission via protocatechuic acid to β-ketoadipic acid (Kurane 1986). The soil and waste-water bacterium *Pseudomonas acidovoruns* was found to degrade diethyl phthalate with a half-life of 10.5 days at 30°C (initial concentration of 3,000 mg/kg) (Kurane et al. 1977). Karegoudar and Pujar (1984b, 1985) isolated two types of bacteria, *Micrococcus varians* and *Bacillus sphaericus,* from industrial waste water and sewage ponds. These bacteria were able to grow aerobically using diethyl phthalate as the sole carbon source. Diethyl phthalate is hydrolyzed by the bacterial enzymes to free phthalic acid via the intermediate monoester (Karegoudar and Pujar 1984a). Other bacteria found in sewage treatment facilities are also able to degrade diethyl phthalate (Gibbons and Alexander 1989).

5. POTENTIAL FOR HUMAN EXPOSURE

Aerobic degradation of diethyl phthalate by acclimated soil and activated sewage sludge microbes was studied by using carbon dioxide (CO_2) evolution. Primary biodegradation (loss of parent ester) of diethyl phthalate was greater than 99% with a lag phase of 2.3 days, and ultimate biodegradation (CO_2 evolution) was 95%. The half-life for the compound under these conditions was 2.21 days (Sugatt et al. 1984). Complete bacterial acclimation to graded concentrations (50 to 410 mg/L) of diethyl phthalate was found in an aerobic, activated sludge system (Tokuz 1991). More than 94% of diethyl phthalate, however, was biodegraded within 1.1 days using semicontinuous activated sludge treatment (O'Grady et al. 1985). Other studies of the aerobic biodegradation of diethyl phthalate indicated that using settled domestic waste water as the microbial inoculum in the static culture flask test and 5 or 10 mg/L of diethyl phthalate, degradation was complete within 1 week of incubation in the dark (Tabak et al. 1981). Diethyl phthalate was degraded by activated sludge with an estimated half-life of 10.5 minutes (Urushigawa and Yonezawa 1979). Investigators found virtually complete primary and ultimate biodegradation of diethyl phthalate using semi-continuous sludge and shake flask procedures, respectively (Monsanto Corporation 1983).

The degradation of diethyl phthalate by sewage sludge bacteria indicated that aerobic degradation is more rapid than anaerobic degradation; however, aerobic degradation is significantly reduced by low dissolved oxygen levels and low temperature. Under less-than-optimal aerobic conditions and anaerobic conditions, facultative bacteria will outcompete aerobic bacteria in degrading diethyl phthalate Zhang and Reardon 1990).

All of the diethyl phthalate added to river water at 25 mg/L was degraded within 6 days, while after 14 days in relatively clean ocean water the degradation rate was between 14% and 20%, and in polluted ocean water the degradation rate was 68% (Hattori et al. 1975). Primary degradation using river die-away procedures was virtually complete (Monsanto Corporation 1983).

Diethyl phthalate was aerobically degraded by two of three marine bacteria isolated from waters near the Mississippi River delta region (Taylor et al. 1981).

More than 98% of diethyl phthalate was degraded (original concentration of 4 mg/L) in less than 8 days by anaerobic sewage sludge (Ziogou et al. 1989). Under anaerobic conditions, diethyl phthalate

was degraded to CO_2 and methane (CH_4) (greater than 75% of theoretical CH_4 production) by a 10% sludge solution from a primary digester and partially degraded (30-75% of theoretical CH_4 production) by a 10% sludge solution from a secondary digester (Shelton and Tiedje 1984). Diethyl phthalate removal was greater than 90% within 1 week with undiluted sludge (Shelton et al. 1984).

In other studies of the anaerobic degradation of diethyl phthalate, municipal sewage sludge mixed with 20 mg/L of diethyl phthalate yielded between 33% and 55% of the theoretical methane production after 6 days of incubation. Higher concentrations of diethyl phthalate (100 and 200 mg/L) strongly inhibited methane production regardless of the length of the incubation period (O'Conner et al. 1989). The degradation of diethyl phthalate under anaerobic conditions appears to be, in part, dependent on the type of sewage sludge used. A comparison of anaerobic degradation using two municipal sludges showed that one did not mineralize diethyl phthalate after 8 weeks of incubation, whereas a second sludge showed 32% of theoretical methane production in 4 weeks (Horowitz et al. 1982).

5.3.2.3 Soil

Degradation of diethyl phthalate applied to soil at an initial concentration of 1 mg/kg was 4% at 24 hours, 11% at 48 hours, 40% at 72 hours, and 86% at 120 hours. Addition of landfill leachate to the soil significantly increased the degradation rate with all of the diethyl phthalate being degraded within 72 hours (Russell et al. 1985). The biodegradation rate of an aerobic microbial strain in batch fermentation and sandy soil column experiments was facilitated at 25°C (relative to 5°C or 15ºC) and at dissolved oxygen concentrations of 0.85 to 8.5 mg/L (Reardon and Zhang 1992). The degradation kinetics of a facultative strain were inhibited by anaerobic conditions, unaffected by the dissolved oxygen level, and greater at 15°C than at 25°C under aerobic conditions. Differences in biodegradation kinetics were related to the tighter adsorption of the facultative strain.

A 2-year study of slow-rate land treatment using waste waters containing diethyl phthalate found that diethyl phthalate was relatively nonvolatile during spray application. Applied at a rate of 56 µg/L to sandy loam and silty loam soils, diethyl phthalate accumulated in the top 5 cm of sandy loam soils to concentrations of 1,000-6,700 ng/g and on the surface of the silty soil from below the detection limit (1 ng/g) to 2,200 ng/g dry soil. Diethyl phthalate was present in greater concentrations at greater

depths in the sandy soil. Although diethyl phthalate was detectable in each soil type down to a depth of 150 cm, it was not detected to any significant degree in the percolate from either soil. Diethyl phthalate did not appear to volatilize from the soil during spray application of the waste water to the soil or thereafter (Parker and Jenkins 1986).

The soil fungus *Fusarium 2P3* was able to use diethyl phthalate as a growth substrate with growth being constant after 4 days of incubation (Klausmeier and Jones 1960).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Analytical data regarding diethyl phthalate concentrations in environmental media must be interpreted with caution, because of the extensive contamination of laboratory glassware with these chemical agents (Lopez-Avila et al. 1990).

5.4.1 Air

Diethyl phthalate has been measured in the indoor air of a telephone switching office and in outdoor air in Newark, New Jersey, at concentrations ranging from 1.60 to 2.03 μg/m^3 and from 0.40 to 0.52 μg/m^3, respectively, during a 43-day sampling period (Shields and Weschler 1987).

5.4.2 Water

Diethyl phthalate was found in the finished drinking water of 6 of 10 U.S. cities at concentrations of 0.01 μg/L (Seattle, Washington; Philadelphia, Pennsylvania; New York, New York), 0.04 μg/L (Lawrence, Kansas), 0.1 μg/L (Cincinnati, Ohio), and 1.0 μg/L (Miami, Florida) (Keith et al. 1976). Diethyl phthalate was identified but not quantified in the Cincinnati drinking water by reverse osmosis (Kopfler et al. 1977). A survey of 39 public water wells identified diethyl phthalate at a maximum concentration of 4.6 μg/L (EPA 1989).

5. POTENTIAL FOR HUMAN EXPOSURE

The Storage and Retrieval (STORET) database maintained by EPA contains over 80 million data points on water quality. Diethyl phthalate has been found at a median concentration of less than 10 µg/L in 9.9% of the industrial effluent samples and in 3.0% of the ambient water samples. It has also been detected in 10.0% of all sediment samples at a median concentration of less than 500 µg/kg dry weight and in 6.0% of aquatic biota samples at a median concentration of less than 2.500 mg/kg wet weight (Staples et al. 1985).

Water samples taken from Galveston Bay, Texas, contained diethyl phthalate, as well as other phthalate esters, at unspecified levels; they were among the most abundant pollutants found in the samples (Ray and Giam 1984). Surface water samples collected along the length of the Mississippi River contained diethyl phthalate in significant concentrations: 190 ng/L at Lake Itasca, Minnesota (the source of the Mississippi River); 84 ng/L 25 miles below the inflow of the Ohio River at Cairo, Illinois; 350 ng/L 20 miles below Memphis, Tennessee; and 63 ng/L in the industrial corridor in New Orleans, Louisiana (DeLeon et al. 1986). Diethyl phthalate concentrations ranged from less than 1 ng/L to 430 ng/L in subsurface water samples from North Sea estuaries that had been polluted by industrial waste (Law et al. 1991). Diethyl phthalate was also detected at 0.7 µg/L in ebb tide water of the Inner Harbor Navigation Canal of Lake Pontchartrain, Louisiana (McFall et al. 1985b).

Diethyl phthalate has been detected in the treated waste waters from various manufacturing facilities: textile manufacturing plants at 3.2 µg/L diethyl phthalate (Walsh et al, 1980); a tire manufacturing plant at 60 µg/L (Jungclaus et al. 1976); and pulp and paper manufacturers at 50 µg/L (Brownlee and Strachan 1977; Voss 1984). River water samples from the lower Tennessee River taken below the Calvert City, Kentucky, chemical complex were found to have 11.2 µg/L diethyl phthalate (Goodley and Gordon 1976). Diethyl phthalate was detected at 21 ng/L in tap water from the Kitakyushu area of Japan. Sources were considered to be domestic sewage and industrial waste (Akiyamaet al. 1980). River water samples and sewage effluent collected in 1984 from the Rivers Irwell and Etherow near Manchester, England, contained 0.4-0.6 µg/L of diethyl phthalate (Fatoki and Vernon 1990). Cooling water discharges from electric generating plants along the California coast contained diethyl phthalate in both chlorinated effluents (0.10 µg/L) and unchlorinated effluents (0.01 µg/L). Ocean samples taken 1 km from the discharge site contained 0.06 µg/L of diethyl phthalate (Grove et al. 1985). The

Nationwide Urban Runoff Program, conducted in 1982, detected diethyl phthalate in 4% (3 locations) of 86 samples at concentrations of 0.5-l 1.0 µg/L (Cole et al. 1984).

Diethyl phthalate was found in 28 of 47 waste-water samples taken from a Canadian coal mine with 6 of the positive samples having concentrations exceeding 10 µg/L. Diethyl phthalate was also found in sediments associated with the mine at concentrations of between 5 and 30 µg/g (Atwater et al. 1990).

Diethyl phthalate has been detected in sediment samples taken from the Chesapeake Bay at concentrations ranging from 11 to 42 µg/kg. A sediment sample taken from the Chester River (which flows into the Chesapeake Bay) contained 26 µg/kg, and a sediment sample from a waste-water holding pond adjacent to a plasticizer manufacturing plant outfall near the river had less than 100 µg/kg (Peterson and Freeman 1982a). Further investigation of the Chester River to determine if a plasticizer manufacturing plant was responsible for elevating concentrations of phthalate esters in the river showed that although diethyl phthalate concentrations ranged from 11 to 44 µg/kg, concentrations could not be correlated with intentional or unintentional discharges from the plant (Peterson and Freeman 1984).

Sediment samples taken from tributaries of the Susquehanna River ranged from just above background to 35 µg/kg diethyl phthalate (Russell and McDuffie 1983). Diethyl phthalate has also been detected in sediment from the San Luis Pass in Galveston Bay, Texas, at an average concentration of 5 µg/kg dry weight (Murray et al. 1981). Sediment samples from the Inner Harbor Navigation Canal and Chef Menteur tributary to Lake Pontchartrain, Louisiana, contained diethyl phthalate at concentrations of 25 µg/kg and 65 µg/kg dry weight, respectively (McFall et al. 1985a).

Sediment core samples taken from the Chesapeake Bay below Baltimore Harbor, Maryland, contained diethyl phthalate at levels that reflected increasing water concentrations as a result of industrial production of phthalates. The sample taken closest to Baltimore had diethyl phthalate concentrations of 19 µg/kg at a core depth corresponding to the years 1923-1929. These levels remained relatively constant until 1963-1968, when the diethyl phthalate level jumped to 35 µg/kg; diethyl phthalate was detected at the surface core level of 42 µg/kg from 1974-1979. A core sample taken further down

the bay at a core depth corresponding to the years 1884-1892 (110-120 cm in depth) had a diethyl phthalate concentration of 3.1 µg/kg. Sediment concentrations increased chronologically until they reached a maximum of 22 µg/kg for the period 1972-1979. Production volumes were correlated (R=0.83) for both the sediment nearest Baltimore and for the more distant sample (R=0.60) (Peterson and Freeman 1982b).

Diethyl phthalate levels in water from the Rhine River in the Netherlands ranged from less than 0.15 to approximately 0.45 µg/L over a 12-day period; on days 7 through 11, diethyl phthalate concentrations in suspended particulate matter from the river stayed relatively constant at 0.1 mg/kg. Water samples and suspended particulate matter from Lake Yssel, also in the Netherlands, contained diethyl phthalate at 0.02-0.08 µg/L and <0.1-0.8 mg/kg, respectively (Ritsema et al. 1989). River water samples and sewage effluent collected in 1984 from the Rivers Irwell and Etherow near Manchester, England, contained 0.4-0.6 µg/L of diethyl phthalate (Fatoki and Vernon 1990).

5.4.3 Soil

No studies were located on the levels of diethyl phthalate found in soil.

5.4.4 Other Environmental Media

Fish collected from Great Lakes tributaries in Wisconsin and Ohio during 1981 had diethyl phthalate in all tissue samples at concentrations of less than 0.02 mg/kg to less than 0.30 mg/kg (DeVault 1985). Lake trout (Salvelinus namaycush) and whitefish (Coregonus culpeaforms) taken from Lake Superior near Isle Royale, Michigan had elevated levels of diethyl phthalate (0.5 and 2.2 µg/g, respectively) compared with lake trout and whitefish taken from other parts of Lake Superior (both values below the level of quantification of 0.001 µg/g wet weight). Fish taken from Siskiwit Lake on Isle Royale, Michigan, a pristine area supposedly unaffected by human activity, also had relatively high concentrations of diethyl phthalate in their tissue, 0.4 µg/g for lake trout and 1.7 µg/g for whitefish (Swain 1978). Diethyl phthalate was detected but not quantified in whole fish taken from 13 Lake Michigan tributaries and Grand Traverse Bay in Michigan (Camanzo et al. 1983).

Oysters collected from the Inner Harbor Navigation Canal and clams from the Chef Menteur and Rigolets tributaries to Lake Pontchartrain, Louisiana, contained 1,100 µg/kg, 450 µg/kg, and 340 µg/kg wet weight diethyl phthalate, respectively (McFall et al. 1985a).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The Total Exposure Assessment Methodology (TEAM) study conducted by EPA using nine New Jersey residents monitored the subjects' exposure to volatile chemicals. Diethyl phthalate was detected in 1 of 8 ambient air samples, 2 of 12 exhaled breath samples, and in 1 of 1 drinking water sample; there was no indication of whether any of the monitoring or breath samples were from volunteers considered to be occupationally exposed nor were the diethyl phthalate concentrations quantified (Wallace et al. 1984).

Based on an average concentration of diethyl phthalate in Toronto, Canada, drinking water of 0.0107 µg/L, the mean human drinking water exposure for the years 1978–1984 was estimated to be 0.0058 mg/year assuming an average consumption of 1.5 L water/day (Davies 1990).

Baked foods packaged in cardboard boxes with cellulose acetate windows (containing 16–17% weight to weight [w/w] diethyl phthalate) had diethyl phthalate concentrations of 1.7–4.5 mg/kg. It was suggested that diethyl phthalate may volatilize from the plastic window to the food without direct contact or be adsorbed in condensate on the window, which would then fall back onto the food (Castle et al. 1988). Diethyl phthalate was quantified from food at concentrations of 0–0.51 mg/kg (Giam and Wong 1987). Based on the levels of diethyl phthalate found in food by Castle et al. (1988), Kamrin and Mayor (1991) estimated a total daily dietary exposure to diethyl phthalate of 4 mg based on a daily ingestion of 1 kg of cellulose-acetate wrapped food containing 4 mg/kg diethyl phthalate. Diethyl phthalate was not detected in the aqueous leachate of solid foam polystyrene (Wu 1991).

Diethyl phthalate is listed as an ingredient in 67 cosmetic formulations at concentrations ranging from ≤0.1% to 50%, although most products contain less than 1% diethyl phthalate. The products may be applied to skin, eyes, hair, and nails, and they may come in contact with mucous membranes and the respiratory tract; contact may be frequent (several times a day) and of prolonged duration (years).

Diethyl phthalate is also approved for use as a component of food-manufacturing equipment and packaging at unlimited concentrations (Anonymous 1985) and in drug product containers (Kamrin and Mayor 1991).

Diethyl phthalate was detected in 42% of the human adipose tissue samples taken from children and adults (cadavers and surgical patients) in the various regions of the United States during 1982 (see table below). Concentrations ranged from below the level of detection (0.20 µg/sample) to a maximum of 0.65 µg/g wet tissue weight (EPA 1986a).

Diethyl Phthalate in Human Adipose Tissue

	Age (years)*		
U.S. region	0–14	15–44	≥45
New England	+	+	+
Middle Atlantic	-+	+-	-
East north central	-+	-+-	-+-
West north central	-	+	++
South Atlantic	--	-++-	-+-
East south central	+	+	-
West south central	+	+-	-
Mountain	-	-	+
Pacific	-		-

* The number of symbols for each age group indicates the number of composite samples analyzed.

+= diethyl phthalate detected in sample at trace or quantifiable level
- = diethyl phthalate not detected

An air sampling survey of three rubber products manufacturing plants in Italy found that diethyl phthalate, although not used as an actual product in any of the processes, was present in the workplace air at all three facilities at concentrations of 0–120 µg/m^3 at a shoe-sole factory; 0–30 µg/m^3 in the vulcanization area of a tire-retreading factory; 0–1 µg/m^3 in the extrusion area of the retreading

factory; and l-3 μg/m^3 in the extrusion area of an electrical cables insulation plant (Cocheo et al. 1983).

The National Occupational Exposure Survey, conducted between 1981 and 1983, estimated that 239,149 workers (including 108,580 women) in 16,408 facilities were exposed to diethyl phthalate in the workplace in 1980 with employees in the personal services (hairdressers, cosmetologists) and health services industries having the greatest potential exposure (NOES 1990). The American Conference of Governmental Industrial Hygienists has established an 8-hour time-weighted average threshold limit value of 5 mg/m3 for diethyl phthalate (ACGIH 1990).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

People receiving medical treatments that involve the use of polyvinyl chloride tubing may be exposed to diethyl phthalate as a result of its leaching from the tubing. Diethyl phthalate was found to be leached from polyvinyl chloride dialysis tubing containing aqueous electrolyte solution, human blood, or bovine plasma perfusates. The tubing was perfused with the aqueous electrolyte solution for 22-96 hours, resulting in a level of diethyl phthalate ranging from 18 to 26 mg/L as determined by ultraviolet spectrometry. Even with only 1 hour of perfusion, diethyl phthalate levels reached 20 mg/L although the levels dropped with extended perfusion time. When the tubing was perfused with either human blood or bovine plasma for 8 hours. infrared spectrometry showed diethyl phthalate levels 2-4 times greater than with water, suggesting that diethyl phthalate has greater solubility in lipid-containing fluids than in inorganic solutions (Christensen et al. 1976).

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 diethyl phthalate is available. Where adequate information is not available, ATSDR, in conjunction with 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 diethyl phthalate.

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 or eliminate 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 may be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of diethyl phthalate are sufficiently well defined to allow assessments of the environmental fate of diethyl phthalate to be made. Therefore, no additional information is needed at this time.

Production, Import/Export, Use, and Release and Disposal. Production, import, use, and release of diethyl phthalate are thoroughly described in the literature. There are no available data reporting U.S. export volumes of diethyl phthalate. The data indicate that the potential for human exposure is considerable and is most likely to occur from inhalation of contaminated air or ingestion of contaminated drinking water or foods. The two methods of disposal mentioned in the literature are landfill and incineration (HSDB 1994). More information on the amounts of diethyl phthalate disposed of by each means and the efficiency of each method would be helpful in estimating potential 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 this information for 1988, became available in May of 1990. This database will be updated yearly and should provide a list of industrial production facilities and emissions. However, diethyl phthalate is not currently included in the Toxics Release Inventory as a reportable chemical.

5. POTENTIAL FOR HUMAN EXPOSURE

Environmental Fate. Diethyl phthalate released to air, water, or soil partitions to sediment or is adsorbed to organic matter in water (EPA 1979, 1989; Tomson et al. 1981; Wolfe et al. 1980a). In soils with low organic content, diethyl phthalate may be relatively mobile and consequently may percolate down to groundwater (Russell and McDuffie 1986). Diethyl phthalate is aerobically biodegraded in soils and with sewage sludge (O'Grady et al. 1985; Sugatt et al. 1984; Tabak et al. 1981; Urishigawa and Yonezawa 1979). It is also biodegraded under anaerobic conditions but at a slower rate (Zhang and Reardon 1990). Up to 75% of the total releases of diethyl phthalate potentially result from low-temperature burning at hazardous disposal sites (HSDB 1994). Volatilization will be slow because of low vapor pressure. Vapors will react with photochemically generated hydroxyl radicals, with an estimated half-life of 22.2 hours at 25°C (HSDB 1994). Further information is needed on the volatilization of diethyl phthalate from plastic and other products and its subsequent transformation in air. This information would be useful in identifying the most important pathways of human exposure to diethyl phthalate.

Bioavailability from Environmental Media. The limited toxicity data available in animals provide indirect evidence that uptake of diethyl phthalate occurs following ingestion (Brown et al. 1978; Lamb et al. 1987; Smyth and Smyth 1962). Additional information is needed on the absorption of diethyl phthalate as a result of inhalation of contaminated air.

Food Chain Bioaccumulation. Diethyl phthalate has been detected in aquatic organisms and has been found to bioconcentrate modestly in these organisms (Camanzo et al. 1983; DeVault 1985; McFall et al. 1985a). The database is, however, too limited to determine a representative range of bioaccumulation potential throughout the food chain. Further data on the accumulation potential for diethyl phthalate, including biomagnification in terrestrial and aquatic food chains, does not seem necessary.

Exposure Levels in Environmental Media. Diethyl phthalate has been detected in ambient and workplace air (Shields and Weschler 1987), drinking water (EPA 1989; Keith et al. 1976; Kopfler et al. 1977), surface waters (Fatoki and Vernon 1990; Ray and Giam 1984; *Staples et al.* 1985*),* sediments (Staples et al. 1985), and food (Castle et al. 1988; Giam and Wong 1987); however, limited

current monitoring data were found. Diethyl phthalate has been detected in the surface waters, groundwater, and soil samples taken at a limited number of NPL sites. Additional information on the concentrations of diethyl phthalate in hazardous waste-site media is needed. This information will be helpful in identifying the most important exposure pathways for populations living near these sites.

Exposure Levels in Humans. Detection of diethyl phthalate in human semen, tissue, and fat has been used as an indicator of exposure to diethyl phthalate (Giam and Chan 1976; Van Lierop and Van Veen 1988; Waliszewski and Szymczymski 1990). Because diethyl phthalate is readily absorbed from the gastrointestinal tract, additional information on the concentration of diethyl phthalate in biological tissue and fluids of populations living in the vicinity of NPL sites would be helpful in assessing the extent to which these populations have been exposed to diethyl phthalate.

Exposure Registries. No exposure registries for diethyl phthalate were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance 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 the exposure to this substance.

5.7.2 On-going Studies

Remedial investigations and feasibility studies currently being conducted at the NPL sites contaminated with diethyl phthalate will add to the database on exposure levels in environmental media and in humans and will contribute information for exposure registries. Investigations at these sites will also increase the current knowledge regarding the transport and transformation of diethyl phthalate at hazardous waste sites. No other long-term research studies regarding the environmental fate and transport of diethyl phthalate or the occupational and general population exposure to this compound were identified.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring diethyl phthalate in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify diethyl phthalate. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect diethyl phthalate in environmental samples are the methods approved by federal 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 refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

No analytical methods were located for measuring diethyl phthalate in the serum, blood, or urine of humans or animals. Gas chromatography (GC), combined with electron capture detection (ECD) or mass spectroscopy (MS), has been used to measure diethyl phthalate in human semen (Waliszewski and Szmczymski 1990), animal fat (van Lierop and van Veen 1988), and animal tissues (Giam and Chan 1976), but the data are too limited to allow a comparison of methods. Because phthalates are so pervasive in plastics and elsewhere in the laboratory environment, rigorous control measures are needed to prevent contamination of the sample and to maintain a low background. These procedures include prewashing columns, use of equipment with purified solvents, and baking at high. temperatures to remove organic materials. Investigators have found that contamination from laboratory glassware limits the analysis of phthalate esters in the parts-per-billion to parts-per-trillion range and recommend concurrent controls for all analytical procedures (Lopez-Avila et al. 1990). Organochlorine pesticides and polychlorinated biphenyls (PCBs) cause interference in diethyl phthalate analysis by ECD, requiring their removal.

Preparation steps include extraction with petroleum ether, followed by Florisil® chromatography (Giam and Chan 1976; Waliszewski and Szymczymski 1990). The detection limit for semen was 0.04 mg/kg, and recovery was excellent (95%) (Waliszewski and Szymczymski 1990). Van Lierop and Van Veen (1988) recovered diethyl phthalate from fat by purging with nitrogen at high temperature, collecting the volatilized material on Tenax®, and extracting with hexane. This method was designed to avoid time-consuming methods for removing residual fat, but the low recovery (l-10%) and high detection limit (10 mg/kg) limit its usefulness to crude qualitative analysis.

Burns et al. (1981) described a method for measuring di-(2-ethylhexyl) phthalate in fish lipids with 79-86% recovery, and suggest it could also be used for measuring diethyl phthalate. Detection is by GC/ECD, with a background of 1 ng/injection. The ability to differentiate among different phthalate esters was sacrificed for excellent sensitivity (0.1 pg/injection) and good recovery (70-l 10%) in a method that involves hydrolyzing all phthalate esters to phthalic acid and converting the acid to bis(2,2,2-trifluoroethyl) phthalate, which has an increased ECD response (Takeshita et al. 1977). Table 6-l summarizes methods available for measuring diethyl phthalate in biological samples.

6.2 ENVIRONMENTAL SAMPLES

Diethyl phthalate in environmental samples is most commonly measured using GC with detection by MS preferred because it is less prone to interference than is ECD. Other detection methods include high-performance liquid chromatography (HPLC) or liquid chromatography with ultraviolet (UV) detection. As with biological samples, rigorous cleaning of reagents and equipment is necessary to prevent contamination. Methods that use a minimum number of steps and minimal amounts of solvents and column materials also help minimize contamination.

Diethyl phthalate can be collected by pumping an air sample through ethylene glycol (Thomas 1973) or directly through an activated Florisil® column (Giam and Chan 1976). Measurements in air can also be done by passive sampling on charcoal, which is less expensive than active sampling but requires much longer sampling times. Reproducibility for the passive sampling technique was

TABLE 6-1. Analytical Methods for Determining Diethyl Phthalate in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Semen	Dry sample; extract with petroleum ether; concentrate; elute from Florisil® column with diethyl ether/petroleum ether; concentrate	GC/ECD	0.04 mg/kg	95%	Waliszewski and Szymczymski 1990
Fat	Purge sample with nitrogen at high temperature; collect on Tenax®; extract with hexane	GC/MS	≈10 mg/kg	1–10%	van Lierop and van Veen 1988
Muscle, liver	Homogenize sample in acetonitrile; extract with methylene chloride/ petroleum ether/salt water; concentrate; elute from Florisil® column with diethyl ether/petroleum ether	GC/ECD	≈30 ng/ injection	No data	Giam and Chan 1976

ECD = electron capture detection; GC = gas chromatograph(y); MS = mass spectrometry

l0-15% of the mean value, and the detection limit was estimated to be 0.2 μg/m^3 (Shields and Weschler 1987). The detection limit for the active sampling techniques was 10 ng per injection, with 90% recovery using ethylene glycol trapping (Giam and Chan 1976; Thomas 1973).

Solid phase extraction (SPE) methods using reverse-phase columns are particularly desirable for analyzing liquid samples because they eliminate the need for large solvent volumes and the resulting potential for contamination (Burkhard et al. 1991; Ritsema et al. 1989). SPE using a membrane impregnated with reverse-phase particles achieved 85-100% recovery (Hagen et al. 1990). Ritsema et al. (1989) found mass selective detection (MSD) much more selective than ECD and reported 85% recovery and a detection limit of 10 ng/L. Other methods involve hexane extraction followed by HPLC or GC. The detection limit of the UV detectors used for HPLC (20 ng/injection) is much higher than that of GC/ECD (0.5 ng/injection) (Payne and Benner 1981). Lopez-Avila et al. (1989) replaced the Florisil® column used in EPA method 3620 (EPA 1986b) with a smaller disposable Florisil®cartridge to reduce background and achieved 96% recovery when cartridges were not spiked with potential interfering agents. The cartridge could be used to separate diethyl phthalate from organochlorine pesticides, diesel hydrocarbons, and corn oil. In a later study, these investigators obtained a 55-70% recovery from a solid matrix, after alumina column cleanup (Lopez-Avila et al. 1991). Method 1625 of EPA's Industrial Technology Division is part of a group of broad-range methods for measuring pollutants in waste water. It includes continuous liquid-liquid extraction, followed by gel permeation chromatography and detection by GC/MS (Telliard 1990). EPA (198la) achieved over 100% recovery using Florisil® or alumina columns and GC/ECD, with a sensitivity of 0.13 ng/injection, but found the method inappropriate for certain waste waters because of high interference.

Sludge, sediment, and soil samples are extracted with moderately nonpolar solvents ands.leaned up by liquid chromatography (Ritsema et al. 1989; Russell and McDuffie 1983). Soxhlet® extraction or extraction using ultrasonication was sometimes used to improve efficiency; some authors found ultrasonic extraction resulted in lower blanks and slightly higher efficiency than Soxhlet® extraction (Peterson and Freeman 1982a; Zurmiihl 1990). Recovery was over 80% for the few techniques where recovery was reported. Sensitivity was reported for only a few of the methods, where it ranged from 0.1 to 5.3 μg/kg. Diethyl phthalate has been detected in cosmetic preparations using liquid

chromatography and UV detection, or by direct injection onto the gas chromatograph with flame ionization detection (FID) (Hancock et al. 1966). Diethyl phthalate was detected in pharmaceutical tablets by thin-layer chromatography (TLC) and HPLC/UV (Cafmeyer and Wolfson 1991). Table 6-2 summarizes methods available for measuring diethyl phthalate in environmental samples.

High temperature continuous counter-current gas-liquid chromatography is an effective methodology for separating mixtures of high boiling point organics (Watabe et al. 1992). At a column temperature of 200°C dimethyl and diethyl phthalates were separated to purities of 99.96% and 99.69% respectively.

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 diethyl phthalate is available. Where adequate information is not available, ATSDR, in conjunction with 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 diethyl phthalate.

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 or eliminate 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 may be proposed.

TABLE 6-2. Analytical Methods for Determining Diethyl Phthalate in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collect on charcoal pad; extract with carbon disulfide; concentrate. Method of CC/MS quantitation not described.	GC/MS	≈ 0.2 µg/m^3	No data	Shields and Weschler 1987
Air	Pump sample through ethylene glycol; extract with hexane; concentrate; elute from Florisil® with diethyl ether	GC/MS	10 ng/injection	>90%	Thomas 1973
Tap water	Collect sample by reverse phase SPE C18 PTFE membrane; elute with acetonitrile	HPLC/UV	<10 µg/L	85–99%	Hagen et al. 1990
Waste water	Extract sample with dichloromethane/hexane; elute from Florisil® or alumina with ether/hexane	GC/ECD; GC/FID	0.1 ng/injection 31 ng/injection	109–116%	EPA 1981a
Effluent	Filter sample; elute from SPE column with methanol/ water; concentrate eluate; separate over reverse-phase HPLC column with methanol/water and collect eluates; concentrate and analyze by CC/MS	GC/MS	1 µg/L	No data	Burkhard et al. 1991

TABLE 6-2. Analytical Methods for Determining Diethyl Phthalate in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water/suspended particulate matter (SPM)	Water samples collected on reverse-phase SPE column, dried, eluted with hexane/ether; SPM collected by continuous flow centrifugation, extracted with acetone/water/hexane, and wash hexane phase with water	GC/MS/SIM	10 ng/L (water) 0.1 mg/kg (SPM)	85% (water) 67% (SPM)	Ritsema et al. 1989
Water, sediment	Water samples extracted with hexane, concentrated, for GLC extracted with isooctane; sediment samples Soxhlet® extracted with acetonitrile	HPLC/UV	20 ng/injection	94-96%	Payne and Benner 1981
		GC/ECD	0.5/injection	95-98%	
		HPLC/UV	20/injection	90-94%	
Soil, sandy loam	Extraction by sonication with methylene chloride-acetone (1+1), concentrate into hexane; with comparative evaluation of sample clean-up on alumina or Florisil® columns	GC/ECD & GC/FID (dual columns, dual detector)	6-60 µg/kg (typical values)	55-70%	Lopez-Avila et al. 1991

TABLE 6-2. Analytical Methods for Determining Diethyl Phthalate in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sewage sludge	Homogenize, freeze-dry and grind sample; extract with methylene chloride using ultrasonication, clean-up on activated alumina and activated Florisil® columns. Transfer into hexane and add to activated alumina column, wash with hexane, hexane/10% CH_2Cl_2 and elute with hexane 15% CH_2Cl_2; add latter to activated Florisil® columns, wash with CH_2Cl_2 and elute with CH_3Cl_2/5% acetone	GC/ECD	No data	80%	Zurmuhl 1990
Landfill leachate, sediment, soil	Extract leachate with methylene chloride; dry; dissolve in hexane; elute from alumina column, after washing, with benzene; elute from silica column in acetone/benzene. Extract soil and sediment samples with hexane/acetone; dry; dissolve in hexane; clean up as above	GC/ECD	1–3 ng/g (soil and sediment) 0.1 µg/L (leachate)	No data	Russell and McDuffie 1983

TABLE 6-2. Analytical Methods for Determining Diethyl Phthalate in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sediment	Dry sample; utrasonically extract with methylene chloride concentrate	GC/MS/SIM	5.3 ng/g	86%	Peterson and Freeman 1982a

ECD = electron capture detection; FID = flame ionization detector; GC = gas chromatograph(y); GLC = gas liquid chromatography; HPLC = high-performance liquid chromatography; MS = mass spectrometry; SIM = selected ion monitoring; SPE = solid-phase extraction; SPM = suspended particulate matter; UV = ultraviolet detection

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. No methods were located for measuring diethyl phthalate or its metabolites in animal or human serum, blood, or urine. Methods are available for determining diethyl phthalate in human semen and animal fat and muscle (Giam and Chan 1976; Van Lierop and Van Veen 1988; Waliszewski and Szymczymski 1990). Because the available data indicate that diethyl phthalate exposure is associated with negligible toxicological potential, additional studies to identify specific biomarkers of exposure appear unnecessary. Consequently, a data need for identifying biomarkers does not exist. However, additional metabolic and/or comparative toxicokinetic studies, recommended in Section 2.9.2 to elucidate high-dose effects, may incidentally reveal a specific biomarker of exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods exist for measuring diethyl phthalate in a variety of environmental media, including air (Shields and Weschler 1987), water (EPA 1989; Fatoki and Vernon 1990; Keith et al. 1976; Kopfler et al. 1977; Ray and Giam 1984; Staples et al. 1985), waste water (EPA 1981a), sludge (Zurmtihl 1990), sediment (Peterson and Freeman 1982a; Russell and McDuffie 1983), soil (Russell and McDuffie 1983), and cosmetics (Hancock et al. 1966). Recovery for most methods is over 80%. Furthermore, the failure to identify signs or symptomology of intoxication suggests that increased analytical sensitivity for biological or environmental samples is unnecessary. Consequently, the refinement of current analytical procedures appears unnecessary.

6.3.2 On-going Studies

No on-going studies regarding analytical methods were located for diethyl phthalate.

7. REGULATIONS AND ADVISORIES

The national and state regulations and guidelines regarding diethyl phthalate in air, water, and other media are summarized in Table 7-l. No international regulations or guidelines were located.

ATSDR has not derived an MRL for diethyl phthalate. EPA (IRIS 1994) assigned diethyl phthalate a reference dose (RfD) of $80x10^{-1}$ mg/kg/day with an uncertainty factor of 1,000 based on decreased growth rate, food consumption, and altered organ weights (Brown et al. 1978). EPA (IRIS 1994) has assigned diethyl phthalate a weight-of-evidence carcinogenic classification of D, which indicates that diethyl phthalate is not classifiable as to human carcinogenicity. Diethyl phthalate is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Right-to-Know Act of 1986" (EPA 1987e, 1988c). Diethyl phthalate is designated as a hazardous substance (EPA 1978, 1987d) and is subject to groundwater monitoring requirements (EPA 1987a, 1987b).

TABLE 7-1. Regulations and Guidelines Applicable to Diethyl Phthalate

Agency	Description	Information	References
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL TWA-skin designation	5.0 mg/m^3	OSHA 1989a (29 CFR 1910.1000); OSHA 1989b
OSHA	Meets criteria for medical records	Yes	OSHA 1987 (29 CFR 1910.20); OSHA 1988
b. Water:			
EPA ODW	Designated a toxic pollutant under section 307(a)(1) of the Federal Clean Water Act and subject to effluent guidelines	Yes	EPA 1977a (40 CFR 401.15); EPA 1977b
c. Food:			
FDA	Indirect food additive for use only as a component of adhesives	Yes	FDA 1977b (21 CFR 175.105); FDA 1977a
d. Other:			
EPA OERR	Reportable quantity	1,000 pounds	EPA 1985a (40 CFR 302.4); EPA 1985b
EPA OSW	Designated as a hazardous substance	Yes	EPA 1978 (40 CFR 116.4); EPA 1987d
	Listing as a hazardous waste: Discarded commercial chemical product off-specification species, container residues, and spill residues thereof	Yes	EPA 1980b (40 CFR 261.33); EPA 1980c
	Listing as a hazardous constituent	Yes	EPA 1988a (40 CFR 261, Appendix VIII); EPA 1988b
	Groundwater monitoring requirement	Yes	EPA 1987a (40 CFR 264, Appendix IX); EPA 1987b

TABLE 7-1. Regulations and Guidelines Applicable to Diethyl Phthalate (continued)

Agency	Description	Information	References
NATIONAL (Cont.)			
EPA OTS	Toxic chemical release reporting: Community Right-to-Know		EPA 1988c (40 CFR 372); EPA 1987e
Guidelines:			
a. Air:			
ACGIH	TLV TWA	5.0 mg/m^3	ACGIH 1990
NIOSH	REL TWA	5.0 mg/m^3	NIOSH 1992
b. Water:	Ambient water quality criteria for protection of human health:		EPA 1980a
	Ingestion of water and organisms	350 mg/L	
	Ingestion of organism only	1.8 g/L	
c. Other:			
	RfD (oral)	8.0×10^{-1} mg/kg/day	IRIS 1990
	Carcinogenic classification	D[a]	
	Unit risk (air)	No data	
	Unit risk (water)	No data	
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable Ambient Air Concentrations		NATICH 1991
California-Montana		0.00	
Connecticut	(8 hours)	5.0×10^{1} µg/m^3	
Florida-Ft. Lauderdale	(8 hours)	5.0×10^{-2} mg/m^3	
Florida-Tampa	(8 hours)	5.0×10^{-2} mg/m^3	
Florida-Pinellas	(8 hours)	5.0×10^{1} µg/m^3	
Florida-Pinellas	(24 hours)	1.20×10^{1} µg/m^3	
Florida-Pinellas	(Annual)	8.00×10^{2} µg/m^3	

TABLE 7-1. Regulations and Guidelines Applicable to Diethyl Phthalate (continued)

Agency	Description	Information	References
STATE (Cont.)			
Maine		0.00	
Maryland		0.00	
Nevada	(8 hours)	1.19×10^{-1} mg/m^3	
New York	(1 year)	1.67×10^{1} µg/m^3	
North Dakota	(8 hours)	5.00×10^{-2} mg/m^3	
Wisconsin	Hazardous air contaminants with acceptable ambient air concentrations	Yes	WAC 1988
b. Water:			
Kansas	Drinking water quality guidelines and standards	350 mg/L	FSTRAC 1988
c. Other:			
Kentucky	Defined as a hazardous waste	Yes	NREPC 1988 (401 KAR 31:040)

[a]D= Not classifiable as to human carcinogenicity

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NIOSH = National Institute for Occupational Safety and Health; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; RfD = Reference Dose; TLV = Threshold Limit Value; TWA = Time-Weighted

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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 (Kd) -- 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.

9. GLOSSARY

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.

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$_{(LO)}$ (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) -- 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$_{(LO)}$ (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$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- 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.

9. GLOSSARY

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.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/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.

9. GLOSSARY

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 CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- 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

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-l 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 endpoints, 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-l and Figure 2-l 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-l) 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 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-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.4, "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 toxaphene 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. 1981.

(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.

(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, 1% NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL 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 18 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 3% 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 (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
					↓		
Cancer							
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

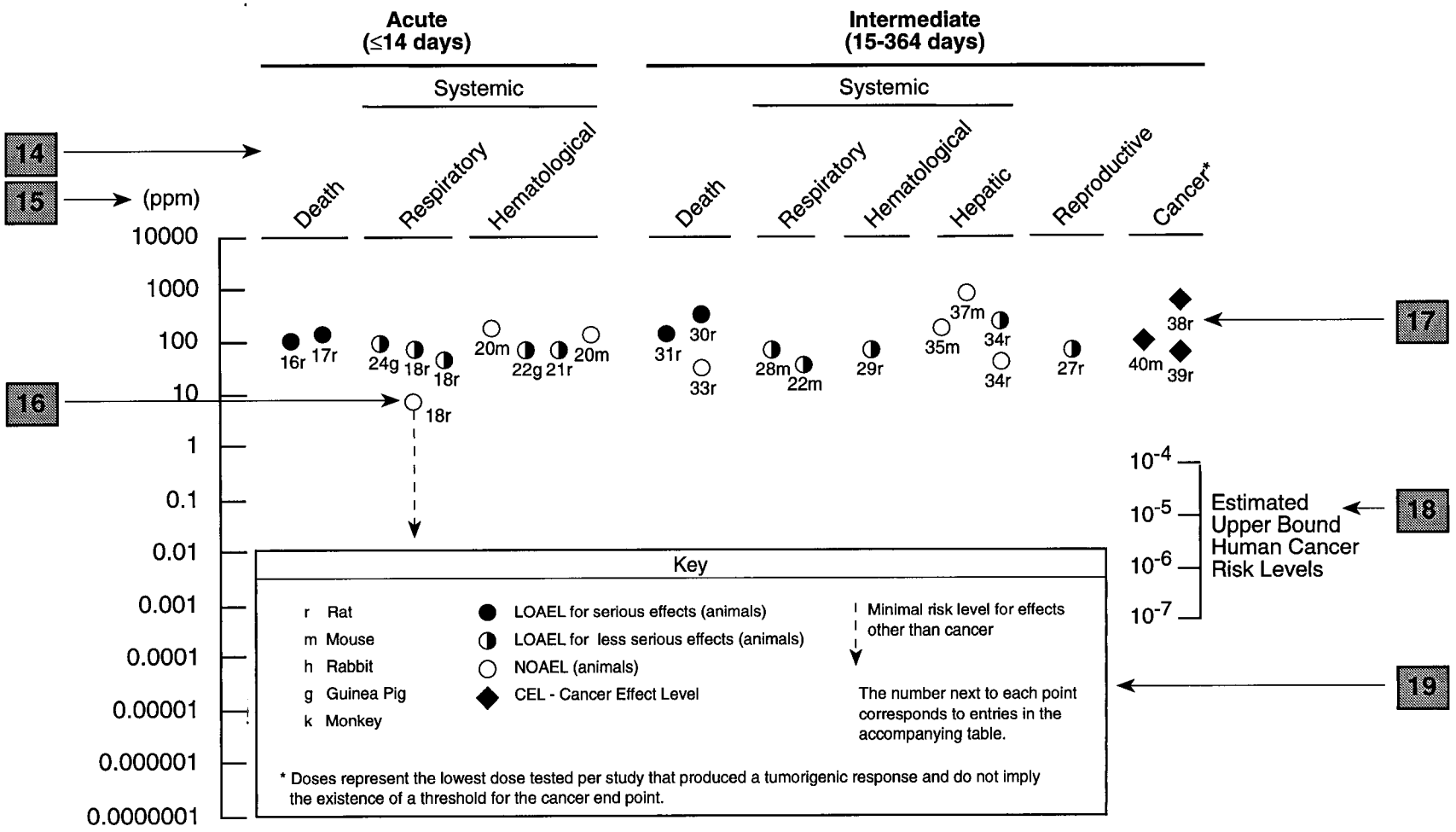
[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.4)

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 endpoints 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 endpoints 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 endpoints (if derived) and the endpoints 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 de familiar with the toxicologic information on which the number is based. Chapter 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Substances,” and 2.7, “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 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 B

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	Federal Register
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
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
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
mmHg	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
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	micron
μg	microgram

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