TOXICOLOGICAL PROFILE FOR DI-*n*-OCTYLPHTHALATE

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

September 1997

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

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

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

FOREWORD

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

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

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

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

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

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

David Satcher, M.D., Ph.D.
Administrator
Agency for Toxic Substances and
Disease Registry

*Legislative Background

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

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Jessilynn B. Taylor, M.S.
ATSDR, Division of Toxicology, Atlanta, GA

Patricia M. Bittner, M.S.
Sciences International, Inc., Alexandria, VA

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 end points.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

PEER REVIEW

A peer review panel was assembled for di-*n*-octylphthalate. The panel consisted of the following members:

1. Bernard D. Astill, Ph.D., Independent Consultant, Spencerport, New York
2. W. Homer Lawrence, Ph.D., Professor, University of Tennessee, Memphis, Tennessee
3. David E. Moody, Ph.D., Research Associate Professor, University of Utah, Salt Lake City, Utah

These experts collectively have knowledge of di-*n*-octylphthalate'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 di-*n*-octylphthalate and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,416 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Di-*n*-octylphthalate has been found in at least 300 of the sites on the NPL. However, the number of NPL sites evaluated for di-*n*-octylphthalate is not known. As EPA evaluates more sites, the number of sites at which di-*n*-octylphthalate is found may increase. This information is important because exposure to di-*n*-octylphthalate may cause harmful health effects and because these sites are potential or actual sources of human exposure to di-*n*-octylphthalate.

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

If you are exposed to a substance such as di-*n*-octylphthalate, many 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, gender, nutritional status, family traits, life-style, and state of health.

1 .1 WHAT IS DI-*n*-OCTYLPHTHALATE?

Di-*n*-octylphthalate, also known as dioctyl phthalate, is a colorless, odorless, oily liquid. It does not evaporate easily. There is no evidence that di-*n*-octylphthalate occurs naturally in

the environment. Di-*n*-octylphthalate is manufactured for many uses. It is commonly used as a plasticizer (a substance added to plastics to keep them soft or more flexible). These plastics are found in products such as carpetback coating, packaging films, medical tubing and blood storage bags, floor tile, wire, cables, and adhesives. Di-*n*-octylphthalate is also used in cosmetics and pesticides. For more information on the chemical and physical properties of di-*n*-octylphthalate, see Chapter 3. For more information on its production and use, see Chapter 4.

1.2 WHAT HAPPENS TO DI-*n*-OCTYLPHTHALATE WHEN IT ENTERS THE ENVIRONMENT?

Di-*n*-octylphthalate may enter the environment in industrial waste waters, air emissions, and solid wastes from manufacturing and processing operations, from evaporation of the compound from plastics, from the burning of plastic products, and by leaking from plastics in landfills into soil or water, including groundwater. Di-*n*-octylphthalate is expected to stick tightly to soil, sediment, and dust particles once it is released to the environment. If released to the atmosphere, the compound may be deposited on the ground or to surface water in rain or dust particles. Small amounts of the compound can build up in animals that live in water, such as fish and oysters. The compound breaks down into other products mainly by the action of microorganisms. Additional ways di-*n*-octylphthalate is transformed into other substances include reaction with sunlight and other chemicals present in the atmosphere, reaction with water, and breakdown of the compound in surface waters by sunlight. For further information on what happens to di-*n*-octylphthalate when it enters the environment, see Chapters 4 and 5.

1.3 HOW MIGHT I BE EXPOSED TO DI-*n*-OCTYLPHTHALATE?

You may be exposed to di-*n*-octylphthalate by eating foods contaminated with any of the compound that has leaked from plastic containers, by eating certain foods, such as fish, that have built up high levels of the compound, and by drinking contaminated water. You may also be exposed to di-*n*-octylphthalate during medical treatments such as blood transfusions

and dialysis that use equipment made of plastics containing di-*n*-octylphthalate. In addition, if you live near a hazardous waste site or an industrial manufacturing or processing facility, you may be exposed through contact with air, water, or soil that may have been contaminated around these sites. Little information is available about the concentrations of di-noctylphthalate in air, water, or soil. The compound has been measured at 0.06-0.94 parts di-*n*-octylphthalate per trillion parts of air (ppt), in rain at 2.6-20 ppt, in river water at l-310 ppt, and in sediment at less than 5-25,000 ppt.

Workers in the chemicals and plastics industries may also be exposed to di-*n*-octylphthalate. The National Occupational Exposure Survey estimated that 10,393 individuals were exposed to the compound in the workplace in 1980. For further information on how you can be exposed to di-*n*-octylphthalate, see Chapter 5.

1.4 HOW CAN DI-*n*-OCTYLPHTHALATE ENTER AND LEAVE MY BODY?

Di-*n*-octylphthalate can enter your body when you drink water or eat food containing it. We do not know if di-*n*-octylphthalate enters your body when you breathe air containing it or when it comes in contact with 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. We do not know how much you will absorb if you eat or drink it. Di-*n*-octylphthalate can also enter your body during medical treatment through the use of plastic tubing or storage bags contaminated with di-*n*-octylphthalate. Once it enters your body, it breaks down into other chemicals and the health effects of some of these chemicals are not well understood. Di-*n*-octylphthalate and its breakdown products will leave your body mostly in your urine, but we do not know how quickly that happens. We do not know if the compound or its breakdown products will remain in the tissues. For more information on how di-*n*-octylphthalate can enter and leave your body, see Chapter 2.

1.5 HOW CAN DI-*n*-OCTYLPHTHALATE AFFECT MY HEALTH?

No information is available regarding the possible human health effects caused by di-*n*-octylphthalate if you breathe, eat, drink, or have skin contact with it. Furthermore, there is no information on the effects of breathing di-*n*-octylphthalate in laboratory animals. Di-*n*-octylphthalate has caused death in some rats and mice given very high doses by mouth. Mildly harmful effects have been seen in the livers of some rats and mice given very high doses of di-*n*-octylphthalate by mouth for short or intermediate durations of time. Brief oral exposures to lower doses of di-*n*-octylphthalate generally caused no harmful effects.

We have no information on the health effects of di-*n*-octylphthalate when applied to the skin of humans for long periods of time. Di-*n*-octylphthalate 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. For more information on the health effects of di-*n*-octylphthalate, please refer to Chapter 2.

We do not know if di-*n*-octylphthalate causes cancer in humans or animals. Unlike other phthalates such as di(2-ethylhexyl)phthalate, di-*n*-octylphthalate does not appear to affect the ability of male animals to father offspring [see ATSDR toxicological profile for di(2-ethylhexyl)phthalate for more information on this chemical]. Some birth defects occurred in newborn rats whose mothers received high doses (approximately 5 grams per kilogram of body weight [5 g/kg]) of di-*n*-octylphthalate by injection during pregnancy. However, humans are not exposed to di-*n*-octylphthalate this way, and no harmful effects on developing fetuses were seen when mice were given this chemical by mouth.

Di-*n*-octylphthalate has not been classified for carcinogenic effects by the Department of Health and Human Services, the International Agency for Research on Cancer, or the EPA.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO DI-*n*-OCTYLPHTHALATE?

Di-*n*-octylphthalate and its principal breakdown products can be measured in urine, blood, ant tissues. However, the information available on these tests is so limited that it is not possible to know if they are specific for di-*n*-octylphthalate, if they can be used to determine how much you were exposed to, if they can predict whether harmful health effects will occur, or how long the test is useful after exposure occurs. These tests are not available in doctors' offices. 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 guidelines for di-*n*-octylphthalate. These are designed to protect the public from the possible harmful health effects of the chemical. However, EPA has recently determined that there is not enough evidence to say that di-*n*-octylphthalate definitely causes harmful effects in humans or to the environment. See Chapter 7 for more information on regulations and guidelines for di-*n*-octylphthalate.

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
(404) 639-6000

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness 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 on the toxicology of di-*n*-octylphthalate. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

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

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

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

The toxicity information presented in this chapter focuses on studies that have identified with reasonable certainty that their test material is di-*n*-octylphthalate or its monoester metabolite, mono-*n*-octylphthalate. Unfortunately, use of the nonspecific term "di-octylphthalate" has contributed to significant confusion and misinformation in the technical and governmental literature with respect to di-*n*-octylphthalate and its much more common isomer, di(2-ethylhexyl)phthalate. Although frequently interpreted as referring to di-*n*-octylphthalate, it is apparent that in almost all cases "di-octylphthalate" and "DOP" have in fact been used as synonyms for di(2-ethylhexyl)phthalate. Throughout this chapter whenever possible, an assessment of the level of certainty that the test compound was di-noctylphthalate will be made.

2.2.1 inhalation Exposure

No studies were located regarding the following health effects in humans or animals after inhalation exposure to di-*n*-octylphthalate:

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 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to di-*n*-octylphthalate.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to di-*n*-octylphthalate.

In animals, the reported oral LD_{50} values are 53,700 mg/kg body weight for male albino rats (Dogra et al. 1987), 13,000 mg/kg for Swiss albino mice (Dogra et al. 1989), and >12,800 mg/kg for mice (Eastman Kodak Company 1978). Dosing was by gavage in these studies. No additional studies were located regarding death in animals after oral exposure to di-*n*-octylphthalate.

LOAEL values from each reliable study for death in each species and duration category are recorded in Table 2-l and plotted in Figure 2- 1.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, musculoskeletal, dermal, or ocular effects in humans or animals after oral exposure to di-*n*-octylphthalate. The systemic effects observed after oral exposure are discussed below. The highest NOAEL values and all LOAEL values from each reliable study for observed systemic effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-1.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in.humans after oral exposure to di-*n*-octylphthalate.

One study reported that feeding di-*n*-octylphthalate to groups of four male Wistar albino rats at average doses of 2,266 mg/kg/day for 3 days, 2,078 mg/kg/day for 10 days, or 1,096 mg/kg/day for 21 days did not result in any gross pathological changes in the pancreas (Mann et al. 1985). No

TABLE 2-1. Levels of Significant Exposure to Di-n-octylphthalate - Oral

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat Albino	NS				53700 M (LD_{50})	Dogra et al. 1987
2	Mouse Swiss	NS				13000 (LD_{50})	Dogra et al. 1989
	Systemic						
3	Rat Sprague-Dawley	4 d 1x/d (GO)	Bd Wt	2800 M			Foster et al. 1980
4	Rat Wistar	3 or 10 d ad lib (F)	Endocr		2000 M (decreased T_4 levels, damaged mitochondria, increased number and size of lysozomes, enlarged Golgi apparatus)		Hinton et al. 1986
5	Rat Sprague-Dawley	14 d 1x/d (GO)	Hepatic		1000 [b] M (17% increase relative liver weight, reduced 7-ethoxy-coumarin O-deethylase activity)		Lake et al. 1986

TABLE 2-1. Levels of Significant Exposure to Di-n-octylphthalate - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
6	Rat Wistar	3 d (F)	Gastro	2266 M			Mann et al. 1985
			Hepatic		2266 M (centrilobular glycogen loss, altered endoplasmic reticulum and bile canaliculi)		
			Renal	2266 M			
			Bd Wt	2266 M			
7	Rat Wistar	10 d (F)	Gastro	2078 M			Mann et al. 1985
			Hepatic			2078 M (necrosis, 19% increase liver weight; centrilobular glycogen loss, fat accumulation; altered endoplasmic reticulum and enzyme activities)	
			Renal	2078 M			
			Bd Wt	2078 M			
8	Rat Wistar	1 wk (F)	Hepatic		1000 M (increased liver weight)		Oishi and Hiraga 1980
			Renal	1000 M			
			Bd Wt	1000 M			
9	Mouse CD-1	14 d (F)	Other	7500	15000 (rough hair coat)		Heindel et al. 1989

TABLE 2-1. Levels of Significant Exposure to Di-n-octylphthalate - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)		LOAEL (effect) Less serious (mg/kg/day)		LOAEL (effect) Serious (mg/kg/day)	Reference
	Immuno/Lymphor								
10	Rat Albino	5 d 1x/d (G)				2685	M	(reduced antibody synthesis)	Dogra et al. 1987
	Reproductive								
11	Rat Sprague-Dawley	4 d 1x/d (GO)		2800	M				Foster et al. 1980
12	Rat Wistar	10 d 1x/d (GO)		2800	M				Gray and Butterworth 1980
13	Rat Wistar	2 d 1x/d (GO)				2000	M	(smooth endoplasmic reticulum vesiculation)	Jones et al. 1993
14	Rat Wistar	10 d (F)		2078	M				Mann et al. 1985
15	Rat Wistar	once (G)				2000	M	(altered testicular mitochondrial function)	Oishi 1990

TABLE 2-1. Levels of Significant Exposure to Di-n-octylphthalate - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
16	Rat Wistar	1 wk (F)			1000 M (decreased testicular zinc levels)		Oishi and Hiraga 1980
	Developmental						
17	Mouse CD-1	Gd 6-13 1x/d (GO)				9780 F (reduced liveborn per litter)	Hardin et al. 1987
	INTERMEDIATE EXPOSURE						
	Systemic						
18	Rat Sprague-Dawley	10 wk ad lib (F)	Hepatic		500 M (mild fatty change, increased gamma glutamyl-transpeptidase + foci)		DeAngelo et al. 1986
19	Rat Wistar	21 d ad lib (F)	Endocr		2000 M (decreased T_4 levels, damaged mitochondria, increased number and size of lysozomes, enlarged Golgi apparatus)		Hinton et al. 1986

TABLE 2-1. Levels of Significant Exposure to Di-n-octylphthalate - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
20	Rat Wistar	21 d (F)	Gastro	1906 M			Mann et al. 1985
			Hepatic		1906 M (increased liver weight; centrilobular glycogen loss, marked fat accumulation, and some necrosis; altered endoplasmic reticulum and enzyme activities)		
			Renal	1906 M			
			Bd Wt	1906 M			

TABLE 2-1. Levels of Significant Exposure to Di-n-octylphthalate - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)		LOAEL (effect) Less serious (mg/kg/day)			LOAEL (effect) Serious (mg/kg/day)		Reference
21	Rat Sprague-Dawley	13 wk ad lib (F)	Hemato	350.1	M						Poon et al. 1995
				402.9	F						
			Hepatic	36.8	M	350.1	M	(cytoplasmic vacuolation, accentuation of zonation, increased ethoxyresorufin-O-deethylase activity)			
				40.8 [c]	F	402.9	F	(cytoplasmic vacuolation, accentuation of zonation, increased ethoxyresorufin-O-deethylase activity)			
			Renal	350.1	M						
				402.9	F						
			Endocr	36.8	M	350.1	M	(reduced follicle size and colloid density in thyroid)			
				40.8	F	402.9	F	(reduced follicle size and colloid density in thyroid)			
			Bd Wt	350.1	M						
				402.9	F						

TABLE 2-1. Levels of Significant Exposure to Di-n-octylphthalate - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)		LOAEL (effect) Less serious (mg/kg/day)			LOAEL (effect) Serious (mg/kg/day)	Reference
22	Mouse CD-1	85-105 d (F)	Hepatic			8640	B	(increased absolute liver weight)		Heindel et al. 1989; Morrissey et al. 1989; NTP 1985
			Renal			8640	F	(increased absolute kidney weight)		
			Bd Wt	8640	B					
23	Mouse CD-1	105 d (F)	Bd Wt	7460						Heindel et al. 1989; Morrissey et al. 1989; NTP 1985
	Reproductive									
24	Rat Wistar	21 d (F)		1906	M					Mann et al. 1985
25	Rat Sprague-Dawley	13 wk ad lib (F)		350.1	M					Poon et al. 1995
26	Mouse CD-1	85-105 d (F)				8640	M	(decreased seminal vesicle weight)		Heindel et al. 1989; Morrissey et al. 1989; NTP 1985
				8640	F					

TABLE 2-1. Levels of Significant Exposure to Di-n-octylphthalate - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
27	Mouse CD-1	105 d (F)		7460			Heindel et al. 1989; Morrissey et al. 1989; NTP 1985
	Developmental						
28	Mouse CD-1	85-105 d (F)		8640			Heindel et al. 1989; Morrissey et al. 1989; NTP 1985
29	Mouse CD-1	105 d (F)		7460			Heindel et al. 1989; Morrissey et al. 1989; NTP 1985

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 3 mg/kg/day; dose divided by an uncertainty factor of 300 (3 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).
[c]Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.4 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ad libitum; B = both sexes; Bd Wt = body weight; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day(s); (GO) = gavage, in oil; Hemato = hematological; LD_{50} = median lethal dose; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; NS = not specified; wk = week(s); x = time(s)

Figure 2-1. Levels of Significant Exposure to Di-*n*-octylphthalate - Oral

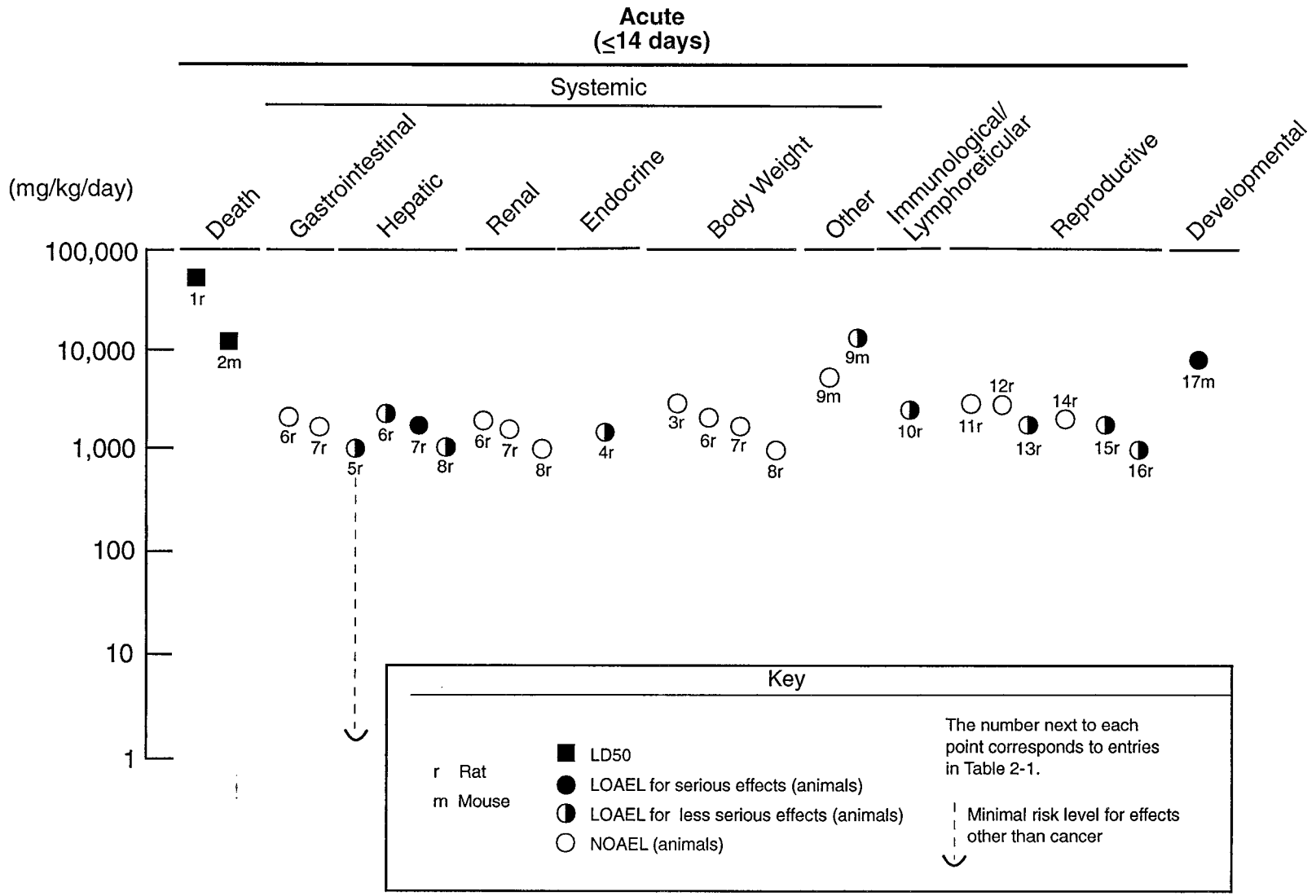
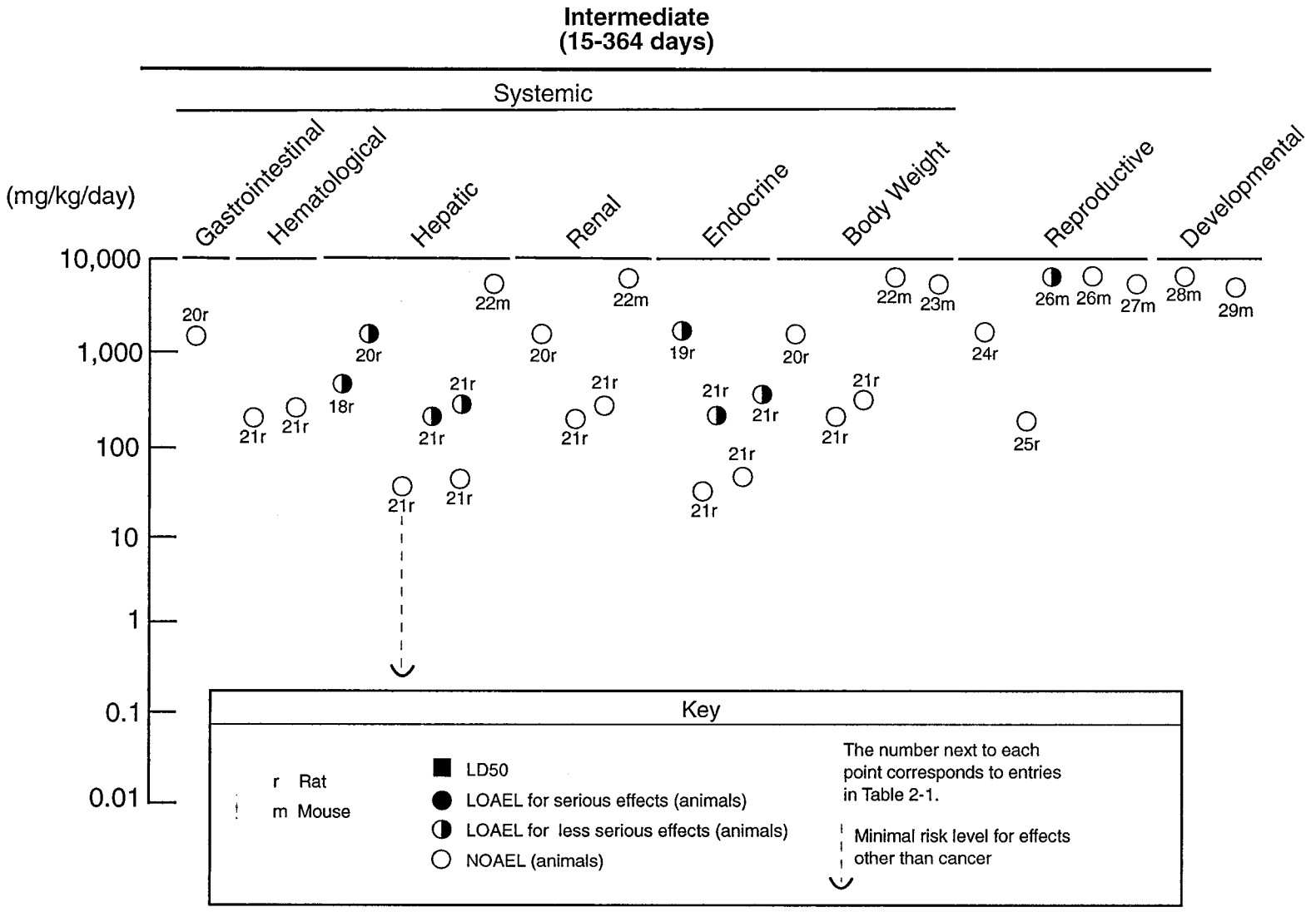


Figure 2-1. Levels of Significant Exposure to Di-*n*-octylphthlate - Oral (continued)



analytical data were reported, but it is reasonably certain that the test compound was di-*n*-octylphthalate (purity was reported to be 99.5%).

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to di-*n*-octylphthalate.

One study in Sprague-Dawley rats (10/sex/group) reported that feeding di-*n*-octylphthalate at concentrations up to 5,000 ppm (350.1 or 402.9 mg/kg/day in males or females, respectively) for 13 weeks did not affect hematological parameters (Poon et al. 1995).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to di-*n*-octylphthalate.

Several studies were located that reported a variety of hepatic effects in rats and mice usually after large oral doses were administered for acute or intermediate durations. These include effects of di-*n*-octylphthalate on liver appearance, structure, and function.

Gross Appearance and Organ Mass. Upon dietary exposure of groups of four male Wistar albino rats to 1,906-2,266 mg/kg/day of di-*n*-octylphthalate for 3-21 days, livers were reported to be pale and greasy in appearance (Mann et al. 1985). When compared with control values, no change in liver weight was observed after 3 days of treatment, although small but significant ($p < 0.01$) increases in relative liver weight (liver weight as a percentage of body weight) were noted after 10 days (4.7% versus 4.0%, or a 19% change from control) and 21 days (4.1% versus 3.2%, or a 28% change from control) of treatment. Similarly, absolute (15%) or relative (16%) liver weights were increased significantly in 10 male Wistar rats after 7 days of dietary exposure to 1,000 mg/kg/day (Oishi and Hiraga 1980). Relative liver weight was significantly increased in 6 male Sprague-Dawley rats after 14 days of exposure by gavage to 1,000 or 2,000 mg/kg/day (Lake et al. 1984, 1986). No changes in absolute or relative liver weights were noted after Sprague-Dawley rats (10/sex/group) were fed concentrations of up to 5,000 ppm (350.1 or 402.9 mg/kg/day in males and females, respectively) in the diet for 13 weeks (Poon et al. 1995).

Male rats, initiated with a single intraperitoneal dose of the carcinogen diethylnitrosamine and then partially hepatectomized, did not experience any liver weight gain after 10 weeks of dietary exposure

to 500 mg/kg/day of di-*n*-octylphthalate (DeAngelo et al. 1986). When exposure was extended to 26 weeks, small increases in absolute liver weight that were not significant ($p < 0.05$) were observed at di-*n*-octylphthalate doses of 250 mg/kg/day (2% increase) and 500 mg/kg/day (8% increase). However, when combined with diminished body weight gains, relative liver weight gains were increased by 5-16% when compared with control values (Carter et al. 1992). These results should be considered independently of the other studies discussed because the animals were surgically altered and chemically treated with diethylnitrosamine.

Dietary exposure for 85-105 days (including lactation during exposure of the dams) to 8,640 mg/kg/day of di-*n*-octylphthalate also induced significant ($p < 0.05$) absolute liver weight gains in male and female CD-l mice (Heindel et al. 1989; Morrissey et al. 1989; NTP 1985). All three of these papers reported the same study; the dose specified here is from the Morrissey et al. (1989) report. A l-week dietary exposure to 1,000 mg/kg/day of mono-*n*-octylphthalate was also reported to induce liver enlargement in seven male Wistar rats (Oishi and Hiraga 1982). Whether those modest liver weight increases resulted primarily from hyperplasia or from hypertrophy is not clear. However, the absence of increased hepatic mitotic activity in two of four rats after di-*n*-octylphthalate exposure in the Mann et al. (1985) study noted above suggests that significant hyperplasia may not be a factor.

Morphology, Histopathology, and Biochemistry. Aside from the pale, greasy appearance noted above, livers from male Wistar rats exposed for 3 days to 2,266 mg/kg/day of di-*n*-octylphthalate in the diet displayed a loss of centrilobular glycogen (Mann et al. 1985). Proliferation and dilation of the smooth endoplasmic reticulum accompanied by some loss of rough endoplasmic reticulum were noted, as were shortened microvilli in some bile canaliculi. No significant changes were noted in parameters associated with hepatic peroxisomal activity (cyanide-insensitive palmitoyl CoA oxidase, α-glycero-phosphate dehydrogenase, and total or peroxisomal catalase activities), plasma membrane integrity (plasma membrane 5'-nucleotidase activity), mitochondrial respiration (succinate dehydrogenase activity), endoplasmic reticular function (glucose-6-phosphatase activity and level of cytochrome P-450), or in the level of nonenzymic reductants. When exposure time was increased to 10 or 21 days (average doses of 2,078 or 1,906 mg/kg/day di-*n*-octylphthalate, respectively), the centrilobular reduction in glycogen became more severe and was associated with fat accumulation and some necrosis. However, the almost total loss of liver glycogen that was observed when using similar doses of di(2-ethylhexyl)phthalate did not occur. Lipid droplets were observed in hepatocytes, along with a possible small increase in the number of peroxisomes; the endoplasmic reticulum morphology

alterations remained apparent. Small but significant ($p < 0.01$ or 0.05) increases were found in hepatic cyanide-insensitive palmitoyl CoA oxidase and peroxisomal catalase activities but not in α-glycerophosphate dehydrogenase or total catalase activities. Significant reductions were noted in 5'-nucleotidase, succinate dehydrogenase, and glucose-6-phosphatase activities compared to the controls. In contrast to di-*n*-octylphthalate treatment, similar doses of di(2-ethylhexyl)phthalate resulted in a dark, enlarged liver, and an initial burst of mitosis was noted at day 3 in two out of four rats. A lesser degree of early centrilobular glycogen loss was noted with di(ethylhexyl)phthalate, but almost total liver glycogen loss occurred after 21 days along with periportal rather than centrilobular fat accumulation, no centrilobular necrosis, pronounced peroxisome proliferation, greater smooth endoplasmic reticulum proliferation, mitochondrial matrix changes, and larger reductions in 5'-nucleotidase, glucose-6-phosphatase, and nonenzymic reductant activities.

Sprague-Dawley rats (10/sex/group) fed 0, 5, 50, 500, or 5,000 ppm of di-*n*-octylphthalate in the diet, corresponding to intakes of 0, 0.4, 3.5, 36.8, and 350.1 mg/kg/day (males) or 0, 0.4, 4.1, 40.8, and 402.9 mg/kg/day (females), for 13 weeks showed significant increases in hepatic ethoxyresorufin-*O*-demethylase activities at the highest dose (Poon et al. 1995). There were histopathologic changes in hepatic architecture noted at 5,000 ppm, however, which included a moderate degree of accentuation of zonation in all animals of both sexes and mild-to-moderate perivenous cytoplasmic vacuolation in 9/10 males and 5/10 females (Poon et al. 1995). These effects were not observed at 500 ppm, which represents the NOAEL. There was no visual increase in peroxisomes noted at any dose level and no changes in activities of either amino-*N*-demethylase or aniline hydrolase.

Rats exposed to dietary concentrations of mono-*n*-octylphthalate equivalent to 1,000 mg/kg/day exhibited a variety of significant alterations in serum lipid composition, reflecting a possible effect on the hepatic metabolism of lipids (Oishi and Hiraga 1982). With respect to control values, serum concentrations of phospholipids and nonesterified fatty acids were increased, while those of triglycerides and total cholesterol were decreased. Levels of free cholesterol, lipoperoxides, and 1ecithin:cholesterol acyltransferase activity were not significantly affected. Mono-*n*-octylphthalate exposure increased palmitic acid content while decreasing stearic acid content in serum phospholipid; increased oleic acid content in serum phospholipid, cholesteryl ester, and triglyceride; decreased linoleic acid content in serum triglyceride; and decreased arachidonic acid content in serum phospholipid. Several other monophthalates were also evaluated, with mono-2-ethylhexylphthalate being generally somewhat more potent than mono-*n*-octylphthalate. The compositional effects of

mono-2-ethylhexylphthalate on serum cholesteryl ester were broader and more pronounced than those of mono-*n*-octylphthalate, while the reverse was true for serum triglyceride (mono-2-ethylhexylphthalate was without significant effect). Such effects could result in part from altered gastrointestinal digestion and absorption of dietary fat, but as suggested by the previously noted accumulation of fat in the liver (Mann et al. 1985), they may reflect altered hepatic metabolism of fatty acids and cholesterol. The toxicological significance of these alterations in lipid metabolism is not known. The study authors noted that the general trend of these serum lipid changes and the attendant increases in liver size are significantly similar to the effects observed after exposure to di(2-ethylhexyl)phthalate (see also ATSDR 1992), thus implicating the monoesters or subsequent metabolites, rather than the diesters, as the active compounds inducing these effects.

Treating male Sprague-Dawley rats with di-*n*-octylphthalate (2,000 mg/kg/day) or mono-*n*-octylphthalate (750 and 1,000 mg/kg/day) by gavage for 14 days (5 rats/dose) did not induce hepatic peroxisome proliferation (Lake et al. 1984). Similar treatment with 1,000 mg/kg/day di-*n*-octylphthalate or 715 mg/kg/day mono-*n*-octylphthalate did not significantly increase (cyanide-insensitive palmitoyl-CoA oxidase and heat-liable enoyl-CoA hydratase) or reduce (*O*-amino acid oxidase) hepatic enzyme activities associated with peroxisome proliferation (Lake et al. 1984, 1986). Both di-*n*-octylphthalate and mono-*n*-octylphthalate significantly reduced ($p < 0.05$) hepatic microsomal-7-ethoxyresorutin *O*-deethylase activity, and di-*n*-octylphthalate reduced 7-ethoxycoumarin *O*-deethylase activity, but neither di-*n*-octylphthalate nor mono-*n*-octylphthalate significantly affected other mixed function oxidase activities (ethylmorphine n-demethylase, lauric acid 11-and 12-hydroxylases), microsomal cytochrome P-450 content, microsomal hemoprotein spectral properties, or sodium dodecyl sulfate-polyacrylamide gel electrophoresis profiles of hepatic whole homogenates and microsomes. Again, these results were substantially different from those obtained with doses of 1,000 mg/kg di(2-ethylhexyl)phthalate and 500 mg/kg of the hypolipidemic drug clofibrate.

Two additional rat studies designed to investigate the reproductive effects of di-*n*-octylphthalate exposure provide another observation on the hepatic effects of di-*n*-octylphthalate. Contrary to what is observed with di(2-ethylhexyl)phthalate, the concentration in liver of the essential element zinc was found not to be significantly reduced after 4 days of gavage exposure to 2,800 mg/kg/day of di-*n*-octylphthalate (Foster et al. 1980), or 7 days of dietary exposure to 1,000 mg/kg/day of di-*n*-octylphthalate (Oishi and Hiraga 1980).

The only oral study located that evaluated the presence of hepatic effects in a species other than rats was a reproductive-developmental toxicity study conducted according to the NTP Continuous Breeding Protocol (Heindel et al. 1989; Morrissey et al. 1989; NTP 1985). F_1 generation CD-l mice (offspring from the fifth litter of a treated F_0 generation) were exposed via lactation to di-*n*-octylphthalate (from dams exposed to approximately 7,460 mg/kg/day) and then via feed after weaning until they were 85-105 days old. The average di-*n*-octylphthalate dose over this period was calculated by the study authors to be 8,640 mg/kg/day. As might be expected from prior rat data, statistically significant increases in absolute liver weight (24%) were noted. The study authors reported that no gross morphological or histopathological alterations were observed in the treated livers. This is despite substantially higher doses and longer treatment times than were used in the rat studies and despite a fourfold lower acute oral LD_{50} reported for mice than for rats (Dogra et al. 1987, 1989). As has been noted for di(2-ethylhexyl)phthalate (ATSDR 1992), the degree and nature of hepatotoxicity resulting from exposure to di-*n*-octylphthalate may vary considerably with species and also with dosage procedures. Dogra et al. (1987, 1989) employed oral gavage with rats and mice, whereas the NTP study employed dietary feeding with mice.

In summary, the liver appears to be a primary target organ for the toxic effects of acute- and intermediate-duration high-dose exposure to di-*n*-octylphthalate (and mono-*n*-octylphthalate), at least in the rat and mouse. Unlike its branched-chain isomer di(2-ethylhexyl)phthalate, di-*n*-octylphthalate presents a liver toxicity profile only weakly suggestive of the hypolipidemic peroxisome proliferators (e.g., clofibrate). Instead, the liver changes associated with exposure to di-*n*-octylphthalate are characterized by marked centrilobular accumulation of fat and loss of glycogen, accompanied by reduced glucose-6-phosphatase, cytoplasmic vacuolation, accentuation of zonation, and some centrilobular necrosis. However, although these effects have been noted in two studies (Mann et al. 1985; Poon et al. 1995), they were not seen in a multigeneration study in mice by NTP (Heindel et al. 1989; Morrissey et al. 1989; NTP 1985) or in other studies in rats (Lake et al. 1984, 1986; Oishi and Hiraga 1980). It should be mentioned here that di-*n*-octylphthalate has been shown to induce additional liver effects associated with preneoplastic alteration; these are discussed below under "Cancer."

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to di-*n*-octylphthalate.

Few animal studies were located that report any observations on the renal toxicity of di-*n*-octylphthalate. In a study examining the effects of di-*n*-octylphthalate on testicular function, rats that had received 2,800 mg/kg/day by gavage for 4 days were observed to have a small (9%) but not statistically significant reduction in kidney zinc concentration when compared with controls (Foster et al. 1980). Total urinary excretion of zinc was reduced to 85% of controls, but again this was not significant. When expressed as a percentage of zinc excretion on day 0 (i.e., prior to di-noctylphthalate administration), the 4-day urinary excretion profile of zinc in the di-*n*-octylphthalate-treated rats was virtually identical to that of controls. No effect on kidney weight was observed. In contrast, these parameters were generally elevated after treatment with n-alkylphthalates that induced testicular pathology (di-*n*-butylphthalate, di-*n*-pentylphthalate, and di-*n*-hexylphthalate; see "Reproductive Effects," below). These findings are supported by another study in rats in which dietary exposure of male Wistar rats for 1 week to 1,000 mg/kg/day of di-*n*-octylphthalate did not affect the concentration of zinc in the kidney (phthalic acid slightly increased it) nor significantly ($p < 0.05$) reduce kidney weight as did di(2-ethylhexyl)phthalate (Oishi and Hiraga 1980). No gross pathological changes were observed in the kidneys of male Wistar rats following 3-, 10-, or 21-day exposure to 2% di-*n*-octylphthalate in the diet (2,266, 2,078, or 1,906 mg/kg/day, respectively) (Mann et al. 1985). No effects on absolute or relative kidney weight were noted when Sprague-Dawley rats of both sexes were fed di-*n*-octylphthalate for 13 weeks at concentrations up to 5,000 ppm (350.1 or 402.9 mg/kg/day in males and females, respectively) (Poon et al. 1995).

One reproductive-developmental toxicity study in CD-l mice also examined the renal effects of di-*n*-octylphthalate exposure (Heindel et al. 1989; Morrissey et al. 1989; NTP 1985). Following the NTP Continuous Breeding Protocol, F_1 mice taken from the last litter of treated F_1 parental mice (7,460 mg/kg/day for 105 days, including the mating period) were exposed for 85-105 days to an average calculated di-*n*-octylphthalate dose of 8,640 mg/kg/day (first via lactation, then feed). Although no gross morphological or histopathological changes in the kidney were noted, absolute kidney weight was significantly ($p < 0.05$) elevated in female (1l%), but not male, mice.

Despite the absence of data on organ function, these limited results suggest that acute or intermediate oral exposure to even very high doses of di-*n*-octylphthalate is not likely to result in substantial renal toxicity.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to di-*n*-octylphthalate.

There is some evidence in animals that suggests that oral administration of di-*n*-octylphthalate may affect the thyroid gland. Serum from four male Wistar rats that were fed di-*n*-octylphthalate at a concentration of 2% in the diet (approximately 2,000 mg/kg/day) in a previous study (Mann et al. 1985) was reassayed (Hinton et al. 1986). After 3, 10, and 21 days of treatment, significant decreases in thyroxine (T_4) levels were noted compared to the controls. T_4 levels were 47%, 59%, and 76% of control values after 3, 10, and 21 days of treatment, respectively. No significant effects on triiodothyronine (T_3) levels were noted compared to the controls (Hinton et al. 1986). In addition, marked ultrastructural changes were noted in the thyroids of these animals, including increases in the numbers and size of lysosomes, enlargement of the Golgi apparatus, and apparent damage to the mitochondria (Hinton et al. 1986). This study was limited, however, in that only one concentration was tested.

Groups of 10 male and 10 female Sprague-Dawley rats that were administered di-*n*-octylphthalate in the diet for 13 weeks at concentrations of 0, 5, 50, 500 and 5,000 ppm, corresponding to intakes of 0, 0.4, 3.5, 36.8, and 350.1 mg/kg/day (males) and 0, 0.4, 4.1, 40.8, and 402.9 mg/kg/day (females) showed reductions in the size of thyroid follicles and mild decreases in colloid density at 5,000 ppm (Poon et al. 1995). Changes in these parameters was also noted at 500 ppm, but it is not whether this concentration represents a LOAEL, because statistical analysis of the data was not performed.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to di-*n*-octylphthalate.

Data from various studies consistently indicate that acute or intermediate oral exposures to high doses (l,000-15,000 mg/kg/day) of di-*n*-octylphthalate do not adversely affect either body weight gain or food consumption in rats or mice (Carter et al. 1992; Heindel et al. 1989; Mann et al. 1985; Morrissey

et al. 1989; NTP 1985; Oishi and Hiraga 1980, 1982). In male Wistar rats receiving di-noctylphthalate at a concentration of 2% in the diet (approximately 2,000 mg/kg/day), food intake was significantly ($p < 0.01$) increased after 3 days when compared with controls (13.7 versus 19.5 g/kg/rat), and body weight was significantly ($p < 0.05$) increased after 10 days relative to controls (204 versus 220 g/rat). By days 11-21, however, the values for both parameters returned to control levels (Mann et al. 1985). Male rats subjected to a single intraperitoneal dose of diethylnitrosamine, partial hepatectomy, and 26 weeks of dietary exposure to 250 or 500 mg/kg/day of di-*n*-octylphthalate apparently experienced small reductions (3-7%) in body weight gain (Carter et al. 1992). Male Wistar rats fed 1,000 mg/kg/day of the monoester mono-*n*-octylphthalate for 1 week were reported to have depressed body weight gains during the first 2 days and reduced body weights at the experiment's end, but quantitative data were not provided (Oishi and Hiraga 1982).

Other Systemic Effects. No studies were located regarding other systemic effects in humans after oral exposure to di-*n*-octylphthalate.

After a 14-day exposure of CD-l mice to 1,800, 3,600, 7,500, or 15,000 mg/kg/day, a rough hair coat was noted in four to six out of eight animals of both sexes at 15,000 mg/kg/day (Heindel et al. 1989; NTP 1985).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans after oral exposure to di-*n*-octylphthalate.

Limited data suggest that di-*n*-octylphthalate can exert immunotoxic effects in rats and mice after acute oral exposure to relatively high doses. Male rats exposed by gavage once per day for 5 days to 0, 2,685, 5,370, or 10,740 mg/kg/day of di-*n*-octylphthalate (acute LD_{50} was 53,700 mg/kg) did not display any signs of overt toxicity, but did exhibit a depletion of cells in the periarteriolar lymphoid sheet of the spleen that the study authors noted as dose dependent, although doses at which these effects were observed were not identified (Dogra et al. 1987). Dose-dependent cellularity changes in the thymus resulted in a loss of distinction between the cortex and the medulla, and germinal center activity was diminished in regional and peripheral lymph nodes. In response to the intraperitoneal injection of sheep red blood cells (SRBC), the number of IgM-producing spleen cells was significantly

($p < 0.001$) reduced to approximately 10% or 5% of the control value in rats exposed to the mid- and high-doses, respectively. There was a concomitant, dose-dependent, 1,000-fold reduction in serum anti-SRBC antibodies. Phagocytic and metabolic activities of peritoneal exudate cells were also reduced by up to 30-40%. When challenged by subcutaneous inoculation of 1,000 larvae from the parasite *Nippostrangylus brasiliensis,* 10-day worm counts were indicated to be significantly elevated by mid- and high-dose treatments (19% and 30%, respectively) when compared with controls. Finally, mortality was increased from 2- to 2.5-fold in rats treated with 10,740 mg/kg/day di-*n*-octylphthalate (versus controls) when they were subsequently challenged with intravascular injections of 125 or 250 pg of lipopolysaccharide endotoxin from *Escherichia coli.*

The immune system of the mouse may also be susceptible to the effects of acute oral exposures to di-*n*-octylphthalate (Dogra et al. 1989). Three-month-old Swiss albino mice were exposed to di-*n*-octylphthalate by gavage for 5 days at 0, 650, or 2,600 mg/kg/day (acute LD_{50} was 13,000 mg/kg). Mice were subsequently exposed by intraperitoneal injection to either encephalomyocarditis virus or the malarial protozoan, *Plasmodium berghei.* Maximum mortality levels were reached 8-10 days after viral infection and were 20% (0 mg/kg/day), 40% (650 mg/kg/day), and 70% (2,600 mg/kg/day). Malarial lethality reached plateau levels 4-l 1 days postinfection of approximately 20% (0 mg/kg/day), 25% (650 mg/kg/day), and 70% (2,600 mg/kg/day), then increased to 55%, 70%, and 85%, respectively, by postinfection day 19. Respective mean survival times were calculated to be 13.50, 12.15, and 6.25 days. During the first 14 days after protozoa1 infection, the percentage of mouse erythrocytes infected with the parasite in the high-dose group was consistently and significantly ($p < 0.01$ or 0.05) higher than in the control group. Significant increases were generally not observed in the low-dose group.

Both of these studies did not contain positive controls, and both omitted experimental details and much quantitative data. In addition, no proof of compound identity was provided and the dose levels might be considered high enough to risk inducing overt or generalized systemic toxicity. However, the authors indicated that no signs of gross or other organ toxicity were observed, and previously discussed studies appear, in general, to indicate only adverse hepatic effects following acute oral exposure to di-*n*-octylphthalate. In combination, these studies suggest that acute oral exposure to high doses of di-*n*-octylphthalate, at least in the rat and the mouse, may result in compromised immune responses to bacterial, viral, protozoan, or other parasitic infection.

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

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to di-*n*-octylphthalate.

Limited data from one study on CD-l mice indicate that acute and intermediate dietary exposures to di-*n*-octylphthalate at doses of up to 15,000 mg/kg/day produced virtually no effect on clinical signs of toxicity (Heindel et al. 1989; Morrissey et al. 1989; NTP 1985). No clinical signs of neurotoxicity were noted after a 14-day exposure to 1,800, 3,600, 7,500, or 15,000 mg/kg/day; rough hair coats were noted at the highest dose. No clinical signs of neurotoxicity were observed in the mice following exposure to 1,820, 3,520, or 7,460 mg/kg/day for 105 days, nor in the offspring of the high-dose group that were exposed via lactation followed by feed for 85-105 days to an average di-*n*-octylphthalate dose of 8,640 mg/kg/day.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to di-*n*-octylphthalate.

The results of several acute- or intermediate-duration rodent studies indicate that the potential of di-*n*-octylphthalate exposure to cause adverse reproductive effects is very low. When male rats were exposed by gavage to 2,800 mg/kg/day of di-*n*-octylphthalate for either 4 or 10 days, no testicular atrophy (weight loss or histological lesions), testicular zinc loss, or weight loss of the prostate or seminal vesicles were observed (Foster et al. 1980; Gray and Butterworth 1980). Such effects were induced by di-*n*-butylphthalate, di-*n*-pentylphthalate, di-*n*-hexylphthalate, and di(2-ethylhexyl)phthalate, but not by the methyl, ethyl, *n*-propyl, or *n*-heptylphthalate diesters. No adverse effects on testis weight or histopathology were found in male rats exposed to up to 5,000 ppm (402.9 mg/kg/day) of di-*n*-octylphthalate in the diet for 13 weeks (Poon et al. 1995). Similarly, no effect on testis weight, gross morphology, or histopathology was found in male rats receiving dietary exposure to approximately 2,000 mg/kg/day for 10 or 21 days (Mann et al. 1985). In another study in which male

rats were fed a diet containing 1,000 mg/kg/day of di-*n*-octylphthalate for 1 week, the absence of effect on absolute and relative testis weight was confirmed, and no effect was found on testicular concentrations of testosterone or dihydrotestosterone; however, a significant (15%, $p < 0.05$) reduction in testicular zinc concentration was observed (Oishi and Hiraga 1980). One or more of these parameters was also altered by di-o-butylphthalate, diisobutylphthalate (DiBP), dimethyl phthalate (DMP), diethyl phthalate (DEP), di(2-ethylhexyl)phthalate, and phthalic acid (PA). These data are insufficient to clarify the precise relationship among testicular atrophy, high testosterone, and low zinc, but the study authors speculated that testicular atrophy may depend on phthalate induction of elevated levels of testosterone in the testis, accompanied by reduced zinc levels in both the testis and the liver.

Some small, but statistically significant ($p < 0.05$), changes in testicular mitochondrial respiratory functions were observed in 35-day-old male rats 6 hours after they had received a single oral dose of 2,000 mg/kg di-*n*-octylphthalate by gavage (Oishi 1990). Oxygen consumption of mitochondrial preparations from the testis during state 3 respiration (succinate respiration in the presence of adenosine diphosphate [ADP]; phosphorylation) was reduced by 20% when compared with untreated control values, and the respiratory control ratio of state 3 to state 4 respiration ("resting" succinate respiration in the absence of ADP), which is a measure of respiration dependency on ADP, was also slightly reduced by 8%. Pyruvate and lactate concentrations were not changed, nor was phosphorylative activity (the state 3 ratio of ADP to oxygen consumption). These effects were generally less extensive than those induced by di(2-ethylhexyl)phthalate treatment. Routine histopathological examination showed no changes in the seminiferous tubule structure in 6-8 week old Wistar rats after single gavage doses of 2,000 mg/kg/day on each of 2 consecutive days (Jones et al. 1993). However, electron microscopic examination revealed vesiculation of the smooth endoplasmic reticulum and increased stacking into parallel cistemae in some Leydig cells, but no mitochondrial swelling or degeneration. This study is limited, however, because the tabular listing of effects noted for di-*n*-octylphthalate in this paper shows no vesiculation of smooth endoplasmic reticulum (Jones et al. 1993).

Finally, one mouse reproductive-developmental toxicity study performed according to the NTP Continuous Breeding Protocol was reported in three papers (Heindel et al. 1989; Morrissey et al. 1989; NTP 1985). Dietary exposure of F_0 generation male and female CD-l mice for 105 days to doses of 0, 1,820, 3,620, or 7,460 mg/kg/day of di-*n*-octylphthalate failed to cause any reduction in fertility index (percent fertile pairs) or number of litters/pair. In contrast, at least one of these parameters was

significantly reduced after exposure to di-*n*-propylphthalate or di-*n*-pentylphthalate (8,600 mg/kg/day of di-*n*-propylphthalate and 2,160 mg/kg/day of di-*n*-pentylphthalate completely inhibited fertility). Similarly, F_1 generation mice exposed via lactation and then feed to an average di-*n*-octylphthalate dose of 8,640 mg/kg/day for 85-105 days exhibited a statistically significant ($p < 0.05$) reduction in seminal vesicle weight, but no significant changes were noted for testis, cauda epididymis, or prostate weights, or for sperm concentration, percent mobile sperm, or percent abnormal sperm. In female mice, estrous cycle length was not altered, and no reproductive tract organ weight or histopathological changes were observed. These findings confirm that di-*n*-octylphthalate has a low potential for inducing reproductive toxicity following oral exposure.

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

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to di-*n*-octylphthalate.

In a preliminary developmental toxicity screening study, female CD-l mice received 9,780 mg/kg/day of di-*n*-octylphthalate by gavage once per day during gestation days 6-13 (Hardin et al. 1987; NIOSH 1983). The following data were recorded: the number of pups born alive; total litter weight, pup survival, and litter weight gain immediately after birth and on postpartum day 3; maternal survival and weight gain from gestation day 6 to postpartum day 3; and the number of viable litters. The test material given was undiluted di-*n*-octylphthalate; the maximum feasible dose was considered to have been administered because an oral LD_{10} (the preferred dose) could not be established due to a lack of toxicity. The di-*n*-octylphthalate group varied significantly ($p < 0.05$) from its concurrent corn oil control group only in reduced number of livebom pups per litter (10.2 ± 2.8 versus 11.5 ± 1.7; 11% less than control) and reduced pup weight gain ($0.6 \pm 0.l$ g versus 0.7 ± 0.2 g; 14% change from control). However, the concurrent control values for these two parameters (especially for the number of liveborn pups per litter) were unusually high, and the authors reported that these two parameters were generally higher than those of other control groups from the same study, thus casting additional uncertainty on the biological relevance of these statistically significant changes.

The only other oral study located that examined developmental effects was the NTP Continuous Breeding Protocol study previously discussed in Section 2.2.2.5 (Heindel et al. 1989; Morrissey et al. 1989; NTP 1985). F_0 generation CD-l mice were exposed to di-*n*-octylphthalate doses of 0, 1,820, 3,620, or 7,460 mg/kg/day for 105 days. F_1 generation mice (from the F_0 high-dose group) were subsequently exposed via lactation and then via feed to an average di-*n*-octylphthalate dose of 8,640 mg/kg/day for 85-105 days. In neither case were any significant effects noted for the number of live pups per litter, the proportion of pups born alive, pup sex ratio, or the live pup mean weight.

The combined results of these two studies indicate that di-*n*-octylphthalate probably has a very low potential to induce developmental toxicity, especially in view of the very high doses that were evaluated. The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2- 1.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to di-*n*-octylphthalate.

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to di-*n*-octylphthalate.

Two studies were located in which rats received di-*n*-octylphthalate dietary exposures of 250 or 500 mg/kg/day for either 10 or 26 weeks (Carter et al. 1992; DeAngelo et al. 1986). Five male rats were first initiated with a single subcarcinogenic intraperitoneal dose of diethylnitrosarnine (30 mg/kg), followed by partial hepatectomy. Di-*n*-octylphthalate caused substantial increases in gamma-glutamyltranspeptidase (GGT) positive liver foci when compared with the controls (e.g., from 3.5 to 20.8 foci/cm^2) or in hepatic levels of marker enzymes for altered cellular foci (GGT and glutathione *S*-transferase [GST]). Only a slight increase (threefold) was observed for carnitine acetyltransferase (CAT) activity, a marker for peroxisome proliferation. In contrast, while inducing CAT activity

37-40-fold, di(2-ethylhexyl)phthalate and mono(ethylhexyl)phthalate actually inhibited the foci-associated parameters. These results, although not definitive, suggest that di-*n*-octylphthalate may promote preneoplastic lesions in the rat liver, probably by a mechanism that does not rely on peroxisome proliferation.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans or animals following dermal exposure to di-n-octylphthalate.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to di-n-octylphthalate.

Dermal and ocular effects observed after dermal exposure are discussed below.

Dermal Effects. No studies were located regarding dermal effects in humans following dermal exposure to di-*n*-octylphthalate.

In a toxicity summary submitted by Eastman Kodak Company (1978), di-*n*-octylphthalate was reported to be a slight skin irritant when applied to the depilatated skin of guinea pigs. However, di-n-octylphthalate was not a skin sensitizer in guinea pigs.

Ocular Effects. No studies were located regarding ocular effects in humans following dermal exposure to di-*n*-octylphthalate.

In a toxicity summary submitted by Eastman Kodak Company (1978), ocular administration of di-n-octylphthalate resulted in slight conjunctival irritation and no cornea1 damage. No further details were provided.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans following dermal exposure to di-*n*-octylphthalate.

Di-*n*-octylphthalate was negative in a skin sensitization test in guinea pigs (Eastman Kodak Company 1978). No further details were provided in this summary report.

No studies were located regarding the following health effects in humans or animals after dermal exposure to di-*n*-octylphthalate:

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals following dermal exposure to di-n-octylphthalate.

2.3 TOXICOKINETICS

No studies were located regarding the toxicokinetics of di-*n*-octylphthalate in humans or animals following inhalation or dermal exposure. Information on the toxicokinetics of di-*n*-octylphthalate in humans following oral exposure is not available. There are studies that provide indirect evidence for the oral absorption of di-*n*-octylphthalate in animals (Albro and Moore 1974; Oishi 1990; Poon et al. 1995); however, quantitative information is lacking on the rate and extent of absorption following oral exposure to di-*n*-octylphthalate. Information on the distribution of di-*n*-octylphthalate is limited to oral studies in rats by Oishi (1990), which reported the identification of mono-*n*-octylphthalate in blood and

testes within 1-24 hours (plasma peak at 3 hours, testes peak at 6 hours) after dosing, and by Poon et al. (1995), which reported di-*n*-octylphthalate residues in liver and adipose tissue. The metabolism of di-*n*-octylphthalate following acute exposure has been studied in animals *in vivo* and *in vitro* (Albro and Moore 1974; Brodsky et al. 1986; Lake et al. 1977), and the data indicate that, like most phthalate esters, di-*n*-octylphthalate can be hydrolyzed at one or both ester linkages to produce the monoester as well as phthalic acid (minor metabolite). As with other phthalates, subsequent oxidation of the remaining arylester to short-chained carboxyls, alcohols, and ketones has been demonstrated. Although one study seems to indicate that urine is the major elimination route of di-*n*-octylphthalate metabolites following oral exposure (Albro and Moore 1974), no quantitative information on the rate and extent of excretion is available. No information is available on the mechanism of action of di-n-octylphthalate with respect to its absorption, distribution, metabolism, or excretion.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding the absorption of di-*n*-octylphthalate in humans or animals following inhalation exposure.

2.3.1.2 Oral Exposure

No studies were located regarding the absorption of di-*n*-octylphthalate in humans following oral exposure.

Evidence of oral absorption in rats is demonstrated in the studies by Albro and Moore (1974), Oishi (1990), and Poon et al. (1995). Forty-eight hours after a gavage dose of di-*n*-octylphthalate, metabolites were detected in the urine. The major metabolite (60% of the metabolites in urine) was derived from the monoester (Albro and Moore 1974). The mono-*n*-octylphthalate metabolite was found in the blood and testes of rats from l-24 hours after oral dosing with peak levels reported at 3 hours (for blood) and 6 hours (for testes) (Oishi 1990). Di-*n*-octylphthalate was found in the liver and adipose tissue of rats after they were fed this compound for 13 weeks in dietary concentrations up to 5,000 ppm, indicating its absorption (Poon et al. 1995). Although there are insufficient quantitative data for estimating the oral absorption rate, di-*n*-octylphthalate appears to be absorbed readily;

however, it may have to be converted to mono-*n*-octylphthalate for intestinal absorption to occur (Lake et al. 1977).

2.3.1.3 Dermal Exposure

No studies were located regarding the absorption of di-*n*-octylphthalate in humans or animals following dermal exposure.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding the distribution of di-*n*-octylphthalate in humans or animals following inhalation exposure.

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of di-*n*-octylphthalate in humans following oral exposure.

Following a single oral dose of 2,000 mg/kg of di-*n*-octylphthalate in rats, mono-*n*-octylphthalate was detected in blood with peak levels observed at 3 hours and in the testes with peak levels observed at 6 hours (Oishi 1990). The biological half-life and mean residence time of mono-*n*-octylphthalate in blood were 3.3 and 5.4 hours, respectively. After 13 weeks of oral exposure of rats to di-*n*-octylphthalate in the diet at concentrations up to 5,000 ppm (350 and 403 mg/kg/day in males and females, respectively), the livers contained di-*n*-octylphthalate residues that were either below or just slightly above the detection limit (<3 ppm) (Poon et al. 1995). The adipose tissue of rats fed 5,000 ppm showed di-*n*-octylphthalate residue levels of 15 ppm (males) and 25 ppm (females). This study is limited in that it did not analyze tissues for the presence of metabolites.

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of di-*n*-octylphthalate in humans or animals following dermal exposure.

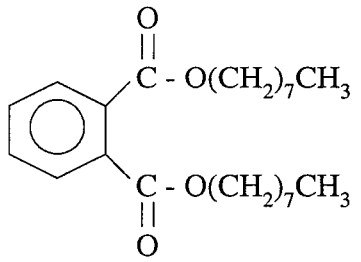
2.3.3 Metabolism

Di-*n*-octylphthalate is readily converted to mono-*n*-octylphthalate, its major metabolite, by hydrolysis of a single ester group. Mono-*n*-octylphthalate is detected in the blood of rats within an hour after oral administration of 2,000 mg/kg di-*n*-octylphthalate (Oishi 1990). Hydrolysis of di-*n*-octylphthalate at both ester linkages to produce phthalic acid (minor metabolite) may also occur, but this conversion does not occur readily.

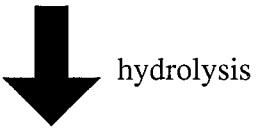
As shown in Figure 2-2, mono-*n*-octylphthalate can undergo ω-, ω-l, α- and β-oxidation to form phthalate monoesters (carboxy, keto, or hydroxy esters), which are the major metabolites detected in the urine (Albro and Moore 1974). Forty-eight hours after the administration of a gavage dose of 559 mg/kg/day of di-*n*-octylphthalate in male CD rats for 2 days, 31% of the administered dose was recovered in the urine as derivatives of the monoester varying in the length of the alkyl side chains (with terminal or subterminal carboxyl, keto, or hydroxyl moieties). The principal urinary metabolite [-$(CH_2)_3$COOH side chain] resulted from an initial ω-oxidation and two β-oxidations of the *n*-octyl side chain (Albro and Moore 1974). The remaining amount detected in the urine was represented by free phthalic acid and mono-*n*-octylphthalate. The unmetabolized parent compound was not detected.

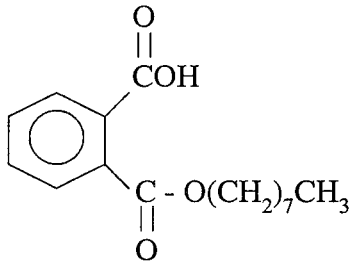
Evidence of the formation of mono-*n*-octylphthalate and phthalate ester metabolites has been shown in *in vitro* studies. The appearance of mono-*n*-octylphthalate was observed with preparations of human small intestine, rat liver and intestine, ferret liver and intestine, and baboon liver and intestine (Lake et al. 1977). However, the amount of phthalic acid and other metabolites in these preparations was either minimal or not detected. The study authors concluded that di-*n*-octylphthalate is probably absorbed primarily as mono-*n*-octylphthalate (Lake et al. 1977). An *in vitro* study reported the formation of five keto acids and two diols when metabolic oxidation of the alkyl groups of di-*n*-octylphthalate was simulated abiotically (Brodsky et al. 1986). Therefore, the *in vivo* and *in vitro* data indicate that major oxidation may occur in the remaining alkyl chain after di-*n*-octylphthalate has been hydrolyzed to the

FIGURE 2-2. Major Metabolic Pathway of Di-*n*-octylphthalate*

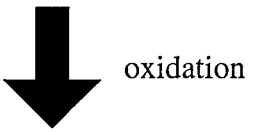


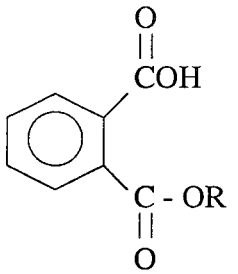
Di-*n*-octylphthalate





Mono-*n*-octylphthalate





R = H (phthalic acid)
= - $(CH_2)_3COOH$
= - $(CH_2)_7COOH$
= - $(CH_2)_6COCH_3$
= - $(CH_2)_6CHOHCH_3$

***Adapted from Albro & Moore 1974**

monoester. It is not known for certain whether di-*n*-octylphthalate is absorbed by the intestine or whether it must first be converted to mono-*n*-octylphthalate.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding the excretion of di-*n*-octylphthalate in humans or animals following inhalation exposure.

2.3.4.2 Oral Exposure

No studies were located regarding the excretion of di-*n*-octylphthalate in humans following oral exposure.

Following gavage administration of 559 mg/kg/day of di-*n*-octylphthalate to rats, metabolites accounting for 31% of the administered dose were detected in the urine at 48 hours postexposure (Albro and Moore 1974).

2.3.4.3 Dermal Exposure

No studies were located regarding the excretion of di-*n*-octylphthalate in humans or animals following dermal exposure.

2.4 MECHANISMS OF ACTION

No studies were located regarding mechanisms of action for absorption or distribution of di-n-octylphthalate in humans or animals following inhalation, oral, or dermal exposure.

Di-*n*-octylphthalate has been shown to be a mild liver toxin at high doses in acute- and intermediate-duration studies in rodents. While the mechanism of action for these hepatic effects is not known, din-octylphthalate does not appear to behave like other phthalate esters such as di(2-ethylhexyl)phthalate, which have been shown to be hypolipidemic peroxisome proliferators. Instead, the liver changes

associated with exposure to di-*n*-octylphthalate are characterized by marked centrilobular accumulation of fat and loss of glycogen, accompanied by reduced glucose-6-phosphatase activity and some centrilobular necrosis. However, these effects have been noted in only one study (Mann et al. 1983, and were not seen in the multigeneration study in mice by NTP (Heindel et al. 1989; Morrissey et al. 1989; NTP 1985) or other studies in rats (Lake et al. 1984, 1986; Oishi and Hiraga 1980).

2.5 RELEVANCE TO PUBLIC HEALTH

Populations living in areas surrounding hazardous waste sites may be exposed to di-*n*-octylphthalate primarily via ingestion of drinking water. Other possible routes of exposure are inhalation of contaminated air or 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 di-n-octylphthalate occurs through the use of consumer products containing it. For example, exposure to di-*n*-octylphthalate can occur in people receiving medical treatments that involve the use of polyvinyl chloride tubing from which di-*n*-octylphthalate can leach. Exposure of the general population can also occur by ingestion of contaminated foods into which di-*n*-octylphthalate has leached from packaging materials, by ingestion of contaminated seafood, by drinking contaminated water, or by inhalation of contaminated air. Occupational exposure to di-*n*-octylphthalate can occur in industrial facilities where it is used in the manufacture of plastics or consumer products.

No information is available on the possible health effects of di-*n*-octylphthalate in humans. The liver is the only target organ that has been identified for di-*n*-octylphthalate in animals following acute- and intermediate-duration oral and parenteral exposure. Acute parenteral studies in animals provided data that suggest that di-*n*-octylphthalate may have adverse effects on the immune system, but the relevance of this route of exposure to humans exposed to di-*n*-octylphthalate at hazardous waste sites is not known. Di-*n*-octylphthalate does not appear to induce reproductive toxicity as do other phthalate esters [e.g., di(2-ethylhexyl)phthalate], and oral developmental toxicity studies with di-*n*-octylphthalate have yielded negative results. A decrease in fetal weight and an increase in the incidence of visceral malformations were noted in the offspring of rats administered high doses of di-*n*-octylphthalate by intraperitoneal injection, but the relevance of this study to humans is not known. The only available data on the potential carcinogenicity of di-*n*-octylphthalate suggest that it may be a tumor promoter, but nothing is known about the ability of this compound to induce cancer by itself. *In vitro*

genotoxicity data indicate that di-*n*-octylphthalate is not genotoxic, but there is no information on the *in vivo* genotoxic potential of this compound.

Minimal Risk Levels for Di-n-octylphthalate

Inhalation

No inhalation MRLs were derived for di-*n*-octylphthalate. No data exist on the effects of acute-, intermediate-, or chronic-duration inhalation exposure to di-*n*-octylphthalate.

Oral

Since no human studies were available, animal studies were used for the derivation of the MRL.

- An MRL of 3 mg/kg/day has been derived for acute oral exposure to di-*n*-octylphthalate. This MRL is based on liver effects observed in rats administered di-*n*-octylphthalate via gavage at a dose of 1,000 mg/kg/day (Lake et al. 1986). The hepatic effects consisted of a statistically significant ($p<0.01$) 17% increase in relative liver weight and a statistically significant ($p<0.05$) reduction in enzyme (7-ethoxycoumarin *O*-deethylase) activities. The LOAEL was divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability). The choice of liver toxicity as the basis for the acute oral MRL is supported by necrosis and mild hepatic fatty changes seen in other acute- and intermediate-duration studies in rats (DeAngelo et al. 1986; Lake et al. 1984; Mann et al. 1985; Poon et al. 1995).

- An MRL of 0.4 mg/kg/day has been derived for intermediate-duration oral exposure to di-n-octylphthalate. This MRL is based on a NOAEL of 40.8 mg/kg/day for liver effects that were observed in rats fed di-*n*-octylphthalate in the diet at a dose of 350.1 mg/kg/day (males) or 402.9 mg/kg/day (females) (Poon et al. 1995). These hepatic effects consisted of a statistically significant ($p<0.05$) increase in hepatic ethoxyresorufin-0-deethylase activity and histological changes in hepatic architecture, including accentuation of zonation and perivenous cytoplasmic vacuolation. Thyroid toxicity (decreased colloid density and reduced follicle size) was also noted at this concentration. The NOAEL was divided by an uncertainty factor of 100 (10 for

extrapolation from animals to humans and 10 for human variability). Support for the use of hepatic toxicity as the basis of the intermediate MRL is provided by other studies that show necrosis and other fatty changes after acute- and intermediate-duration exposure of rats (DeAngelo et al. 1986; Lake et al. 1984, 1986; Mann et al. 1985).

No chronic oral MRLs were derived for di-*n*-octylphthalate because no reliable data exist on adverse effects of chronic-duration oral exposure to di-*n*-octylphthalate.

Death. No studies were located regarding death in humans after exposure to di-*n*-octylphthalate. LD_{50} values in rodents have been reported for di-*n*-octylphthalate following both oral and parenteral administration. Oral LD_{50} values are reported to be 53,700 mg/kg for rats (Dogra et al. 1987) and 13,000 mg/kg for mice (Dogra et al. 1989). The intraperitoneal LD_{50} in rats is >48,900 mg/kg (Singh et al. 1972). These values indicate that di-*n*-octylphthalate is relatively nonlethal and should not present a risk for death in individuals exposed to this compound in the vicinity of hazardous waste sites.

Systemic Effects

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate. No studies were located regarding gastrointestinal effects in humans following oral exposure to this compound.

No pathological changes of the pancreas were exhibited by rats following intermediate-duration exposure to di-*n*-octylphthalate in the diet (Mann et al. 1985). The available information is insufficient to assess whether adverse gastrointestinal effects are likely to occur in humans exposed to di-*n*-octylphthalate in the vicinity of hazardous waste sites, but the limited information discussed above suggests that such effects are unlikely.

Hematological Effects. No studies were located regarding hematological effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate. No studies were located regarding hematological effects in humans following oral exposure to this compound.

The data from one intermediate-duration oral study in rats suggests that di-*n*-octylphthalate does not cause any hematological effects (Poon et al. 1995), but due to the limited data available, this cannot be stated with certainty.

Hepatic Effects. No studies were located regarding hepatic effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate. No studies were located regarding hepatic effects in humans following oral exposure to this compound.

Results from acute- and intermediate-duration oral studies in small numbers of rats conducted at relatively high doses suggest that the liver is a target for di-*n*-octylphthalate-induced toxicity. Hepatic effects noted in these studies include gross changes in appearance, small but statistically significant increases in relative organ weight, ethoxyresorufin-*O*-deethylase activity, alteration in the activity of several hepatic microsomal enzymes, loss of centrilobular glycogen, cytoplasmic vacuolation, accentuation of zonation, proliferation and dilation of the smooth endoplasmic reticulum accompanied by some loss of rough endoplasmic reticulum, fat accumulation, and occasional necrosis (Lake et al. 1984, 1986; Mann et al. 1985; Oishi and Hiraga 1980, 1982; Poon et al. 1995). In addition, rats exposed to dietary concentrations of mono-*n*-octylphthalate equivalent to 1,000 mg/kg/day exhibited a variety of significant alterations in serum lipid composition, reflecting a possible effect on hepatic metabolism of lipids (Oishi and Hiraga 1982). However, di-*n*-octylphthalate does not appear to behave like other phthalate esters such as di(2-ethylhexyl)phthalate, which has been shown to be a hypolipidemic peroxisome proliferator. Based on these results, adverse hepatic effects may occur in individuals living in the vicinity of hazardous waste sites if di-*n*-octylphthalate is present at sufficiently high levels in the substances consumed (e.g., water).

Renal Effects. No studies were located regarding renal effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate. No studies were located in humans following oral exposure to this compound.

Limited information obtained from oral studies in rats and mice suggests that exposure to di-n-octylphthalate, even at relatively high doses, does not affect the kidney, as evidenced by a lack of change in kidney weight or kidney gross and microscopic pathology (Foster et al. 1980; Heindel et al. 1989; Mann et al. 1985; Morrissey et al. 1989; NTP 1985; Oishi and Hiraga 1980; Poon et al. 1995), although one study noted increased absolute kidney weight in rats with no gross or microscopic

change in the kidney (Heindel et al. 1989; Morrissey et al. 1989; NTP 1985). Therefore, based on this limited information, it does not appear that exposure to di-*n*-octylphthalate at the levels expected to be present in the vicinity of hazardous waste sites is likely to induce adverse renal effects in humans.

Endocrine Effects. No studies were located regarding endocrine effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate. No studies were located in humans following oral exposure to this compound.

Data from acute- and intermediate-duration studies in rats suggests that di-*n*-octylphthalate may cause adverse effects on the thyroid gland. The effects observed include decreased thryoxine levels, histopathological changes (reduced follicle size and colloid density), and ultrastructural changes (enlargement of lysosomes and Golgi apparatus, mitochondrial damage) (Hinton et al. 1986; Poon et al. 1995). Further data are necessary to determine whether thyroid effects might occur in persons living in the vicinity of hazardous waste sites as a result of exposure to di-*n*-octylphthalate.

Dermal Effects. No studies were located regarding dermal effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate. No studies were located in humans following oral exposure to this compound.

In a toxicity summary submitted by Eastman Kodak Company (1978), di-*n*-octylphthalate was reported to be a slight skin irritant when applied to the depilatated skin of guinea pigs, but not a skin sensitizer in guinea pigs. No further details were provided; however, it does not appear that di-*n*-octylphthalate is likely to cause dermal irritation.

Ocular Effects. No studies were located regarding ocular effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate. No studies were located in humans following oral exposure to this compound.

In a toxicity summary submitted by Eastman Kodak Company (1978), ocular administration of di-n-octylphthalate in guinea pigs resulted in slight conjunctival irritation and no cornea1 damage. No further details were provided; however, it does not appear that di-*n*-octylphthalate is likely to cause ocular irritation.

Body Weight Effects. No studies were located regarding body weight effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate. No studies were located in humans following oral exposure to this compound.

Data from various acute- and intermediate-duration oral studies in rats and mice conducted at relatively high doses indicate that exposure to di-*n*-octylphthalate does not adversely affect body weight gain or food consumption (Carter et al. 1992; Heindel et al. 1989; Mann et al 1985; Morrissey et al. 1989; NTP 1985; Oishi and Hiraga 1980, 1982; Poon et al. 1995).

Other Systemic Effects. No studies were located regarding other systemic effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate. No studies were located in humans following oral exposure to this compound.

Although a rough hair coat was observed in mice fed 15,000 mg/kg/day for 14 days (Heindel et al. 1989; NTP 1985), it is not expected that other systemic signs of toxicity would be observed in individuals exposed to di-*n*-octylphthalate in the area surrounding hazardous waste sites.

Immunological and Lymphoreticular Effects. No studies were located regarding immunological or lymphoreticular effects in humans or animals following inhalation exposure to di-*n*-octylphthalate, or in humans following oral or dermal exposure to this compound.

Limited data in rats and mice suggest that di-*n*-octylphthalate can exert immunotoxic effects following acute oral or parenteral exposure to relatively high doses. These effects are reflected in changes in the weight and morphology of various lymphoreticular organs (thymus, spleen, and lymph nodes), altered activity of humoral antibody-forming cells and cellular mediators of immunity, and reduced resistance to bacterial, viral, protozoan, and other parasitic infection (Dogra et al. 1985, 1987, 1989).

The available information suggests that exposure to di-*n*-octylphthalate may adversely affect immune function in individuals living in the vicinity of hazardous waste sites if the individuals ingest sufficiently high levels. Because of its low vapor pressure, exposure to high levels of di-n-octylphthalate by inhalation is not likely.

Neurological Effects. No studies were located regarding neurological effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate. No studies were located regarding neurological effects in humans following oral exposure to di-*n*-octylphthalate.

No clinical signs of neurotoxicity were noted in acute- and intermediate-duration dietary exposure studies using mice (Heindel et al. 1989; NTP 1985). Although these data are limited, it is not believed that the low-level exposure to di-*n*-octylphthalate that occurs at hazardous waste sites will result in neurotoxicity.

Reproductive Effects. No studies were located regarding reproductive effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate. No studies were located in humans following oral exposure to this compound. However, di-*n*-octylphthalate has been shown to cause significant decreases in human sperm motility *in vitro* (Fredricsson et al. 1993).

The results of several acute- and intermediate-duration oral studies in rodents indicate that the potential of di-*n*-octylphthalate to cause adverse reproductive effects is low. Unlike other phthalate esters such as di(2-ethylhexyl)phthalate, di-*n*-octylphthalate does not appear to adversely affect testicular function or morphology (Foster et al. 1980; Gray and Butterworth 1980; Heindel et al. 1989; Morrissey et al. 1989; NTP 1985; Oishi 1990; Oishi and Hiraga 1980; Poon et al. 1995). However, some ultrastructural alterations in Leydig cells, including vesiculation of the smooth endoplasmic reticulum, were noted in rats administered di-*n*-octylphthalate by gavage on 2 consecutive days (Jones et al. 1993). Leydig cells obtained from rats that were cultured and stimulated by LH to measure cellular integrity by examining testosterone output showed decreased testosterone production when incubated with mono-*n*-octylphthalate, the major metabolite of di-*n*-octylphthalate (Jones et al. 1993). Examination of these cells exposed *in vitro* showed that mono-*n*-octylphthalate caused an increase in filopodial proliferation from the cell stroma and basal lamellar processes, dilatation of the smooth endoplasmic reticulum, and mitochondrial swelling and degeneration. No adverse effects on the female estrous cycle or on any index of reproductive function were seen in a multigeneration study in mice (Heindel et al. 1989; Morrissey et al. 1989; NTP 1985). Thus, it is unlikely that individuals exposed to di-*n*-octylphthalate in the vicinity of hazardous waste sites are at risk for adverse reproductive effects resulting from exposure to this compound.

Developmental Effects. No studies were located regarding developmental effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate. No studies were located in humans following oral exposure to this compound.

The results of two oral studies in mice (one being a multigeneration reproductive toxicity study) indicate that di-*n*-octylphthalate has a very low potential to induce adverse developmental effects, especially in view of the very high doses that were evaluated in these studies (Hardin et al. 1987; Heindel et al. 1989; Morrissey et al. 1989; NIOSH 1983; NTP 1985). No statistically significant and/or biologically significant effects were observed with respect to the incidence of skeletal or visceral malformations in offspring exposed *in utero.* A significant decrease in fetal survival was reported in one study (Hardin et al. 1987) of mice given 9,780 mg/kg/day di-*n*-octylphthalate by gavage during gestation days 6-13. A small but significant decrease in average fetal weight and a significantly increased incidence of gross fetal malformations were observed in the offspring of rats administered 4,890 mg/kg/day of di-*n*-octylphthalate by intraperitoneal injection (Singh et al. 1972). Given that the effects seen following parenteral administration may not be relevant to human exposure (e.g., different metabolism), the available information suggests that adverse developmental effects are not likely to occur in humans exposed to di-*n*-octylphthalate in the vicinity of hazardous waste sites.

Genotoxic Effects. No studies were located that assessed the potential, if any, of di-*n*-octylphthalate to induce genotoxic effects in either humans or animals exposed via the inhalation, oral, or dermal routes. No mammalian cell assays on di-*n*-octylphthalate were found.
There is, however, a relatively sizable database of well-conducted microbial assays. As part of the NTP, a series of 34 phthalates or related compounds, including di-*n*-octylphthalate (98%), were evaluated for their potential to induce reverse gene mutations in the *Salmonella typhimurium*/mammalian microsome preincubation assay (Zeiger et al. 1982, 1985). Concentrations of di-*n*-octylphthalate ranging from 100 to 10,000 ug/plate in either the presence or absence of exogenous metabolic activation derived from Aroclor 1254-induced rat or hamster liver fractions were not mutagenic in *S. typhimurium* TA1535, TA1537, TA98, or TAL00. Similar evidence that di-*n*-octylphthalate is not a mutagen for *S. typhimurium* strains has been reported in other preincubation suspension assays (Seed 1982; Shibamoto and Wei 1986) and in plate incorporation assays (Florin et al. 1980; Goodyear 1981a; Sato et al. 1994; Shibamoto and Wei 1986). Di-*n*-octylphthalate levels ranging from 100 to 2,000 µg/mL (without S9), and 2,000 µg/mL (with

S9, Aroclor 1254-induced rat liver) did not induce deoxyribonucleic acid (DNA) damage in DNA-repair deficient *E. coli* p3478 (Goodyear 1981b). Di-*n*-octylphthalate also showed a negative response in a prokaryotic SOS chromotest assay (Sato et al. 1994). However, the mutagenicity was increased two-fold in the presence of di-*n*-octylphthalate (Sato et al. 1994).

Extracts of waste water, drinking water, soil, or sediment samples collected from various municipal and industrial solid and/or waste water sites were found to be mutagenic in *S. typhimurium* TA98 and TAL00 (Wang et al. 1990). Although di-*n*-octylphthalate (8.9 µg/L) was identified as one the 18 contaminants in the National Bureau of Standards reference sludge sample, several well-characterized mutagens were among the contaminants. It is, therefore, unlikely that the mutagenic activity uncovered in these samples was associated with di-*n*-octylphthalate but rather with the known mutagens that were listed among the 18 contaminants.

Overall, the results of microbial testing indicate that di-*n*-octylphthalate is not a mutagen. Although the database for *in vitro* genetic toxicology testing is limited, the majority of reported studies were well conducted and showed a high degree of concordance. Based on the available information, there is sufficient valid *in vitro* data to conclude that di-*n*-octylphthalate is devoid of genotoxic activity in bacterial test systems. No conclusions can be reached regarding potential effects on other systems *in vitro* or *in vivo.*

Summarized findings from the *in vitro* genotoxicity studies are presented in Table 2-2.

Cancer. No studies were located regarding cancer in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate, and no studies were located in humans following oral exposure to this compound.

Rats exposed to di-*n*-octylphthalate in the diet for either 10 or 26 weeks following a single subcarcinogenic intraperitoneal injection of diethylnitrosamine and partial hepatectomy exhibited increases in GGT-positive liver foci that were not associated with peroxisome proliferation (Carter et al. 1992; DeAngelo et al. 1986). These results suggest that di-*n*-octylphthalate may be effective in promoting preneoplastic lesions in the rat liver, probably by a mechanism that does not rely on peroxisome proliferation.

TABLE 2-2. Genotoxicity of Di-*n*-octylphthalate *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium (TA1535, TA1537, TA98, TA100)	Gene mutation	–[a]	–[a]	Zeiger et al. 1982, 1985
S. typhimurium (TA100)	Gene mutation	–[a]	–[a]	Seed 1982
S. typhimurium (TA98, TA100)	Gene mutation	–[a,b]	–[a,b]	Shibamoto and Wei 1986
S. typhimurium (TA98)	Gene mutation	–[b]	–[b]	Florin et al. 1980
S. typhimurium TA1535, TA1537, TA98, TA100)	Gene mutation	–[b]	–[b]	Goodyear Tire and Rubber Co. 1981a
S. typhimurium (TA98)	Gene mutation	–[b]	–[b]	Sato et al. 1994
Escherichia coli (W3110 [poLA$^+$], p3478 [poLA$_1^-$] DNA)	DNA damage	–[a]	–[a]	Goodyear Tire and Rubber Co. 1981b
E. coli (PQ37)	SOS induction	–	–	Sato et al. 1994

[a]Liquid suspension/preincubation assay
[b]Plate incorporation assay

– = negative result; DNA = deoxyribonucleic acid

The carcinogenic potential of di-*n*-octylphthalate has not been categorized by either IARC, NTP, or EPA.

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (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 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 di-*n*-octylphthalate are discussed in Section 2.6.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (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 not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by di-*n*-octylphthalate are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Di-*n*-octylphthalate

Animal studies have shown that di-*n*-octylphthalate metabolites (primarily the corresponding phthalate monoesters) can be measured in the urine of rats orally exposed to di-*n*-octylphthalate. Therefore, these phthalate monoesters could be useful biomarkers of exposure. There are no other known biomarkers of exposure to di-*n*-octylphthalate.

2.6.2 Biomarkers Used to Characterize Effects Caused by Di-*n*-octylphthalate

No biomarkers of effects caused by di-*n*-octylphthalate have been identified in humans or animals.

2.7 INTERACTIONS WITH OTHER SUBSTANCES

No studies have been identified that investigated the effects of exposure to di-*n*-octylphthalate together with other chemicals. An *in vivo* assay using *S. typhimurium* TA98 showed that di-*n*-octylphthalate enhanced the mutagenicity of two tryptophan pyrolysis products, which is suggestive of increased mutagenic activity in high-temperature cooking if di-*n*-octylphthalate is present (Sato et al. 1994). .

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to di-*n*-octylphthalate than will most persons exposed to the same level of di-*n*-octylphthalate in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters may result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting

end-product metabolites). 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.

Studies in animals suggest that, unlike some other phthalate esters, the potential for adverse reproductive or developmental effects following exposure to di-*n*-octylphthalate by the route most relevant to human exposure (oral) is very low (Foster et al. 1980; Gray and Butterworth 1980; Hardin et al. 1987; Heindel et al. 1989; Mann et al. 1985; Morrissey et al. 1989; NIOSH 1983; NTP 1985; Oishi 1990; Oishi and Hiraga 1980). Therefore, it does not appear that individuals of child-bearing age or embryos/fetuses are likely to be unusually susceptible to the effects of di-*n*-octylphthalate. No other information is available on populations with above-average susceptibility to di-*n*-octylphthalate.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section describes clinical practice and research concerning methods for reducing toxic effects of exposure to di-*n*-octylphthalate. 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 di-n-octylphthalate. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.9.1 Reducing Peak Absorption Following Exposure

Following dermal exposure to di-*n*-octylphthalate, it has been suggested that the skin be washed immediately with copious amounts of soapy water (Stutz and Ulin 1992). If the eyes are exposed to the liquid or vapor, it has been suggested that they be thoroughly flushed with water. Following ingestion of di-*n*-octylphthalate, it has been suggested that one to two glasses of water should be administered (Stutz and Ulin 1992).

2.9.2 Reducing Body Burden

Administration of activated charcoal as an absorptive surface for di-*n*-octylphthalate has been suggested (Stutz and Ulin 1992). If ingestion of large amounts of di-*n*-octylphthalate 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 (Stutz and Ulin 1992).

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

Di-*n*-octylphthalate has been shown to be a liver toxin at high doses in acute- and intermediate-duration animal studies. Di-*n*-octylphthalate does not appear to behave like other phthalate esters, such as di(2-ethylhexyl)phthalate, which have been shown to be hypolipidemic peroxisome proliferators. Rather, its effects on the liver are more characteristic of other "classic hepatotoxins" (Lake et al. 1984, 1986; Mann et al. 1985). However, the specific mechanism(s) of action for inducing the hepatotoxic effects of di-*n*-octylphthalate is not known. Therefore, there are currently no methods available for interfering with the mechanism of action for the toxic effects of di-*n*-octylphthalate.

2.10 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of di-*n*-octylphthalate 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 di-*n*-octylphthalate.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.10.1 Existing Information on Health Effects of Di-*n*-octylphthalate

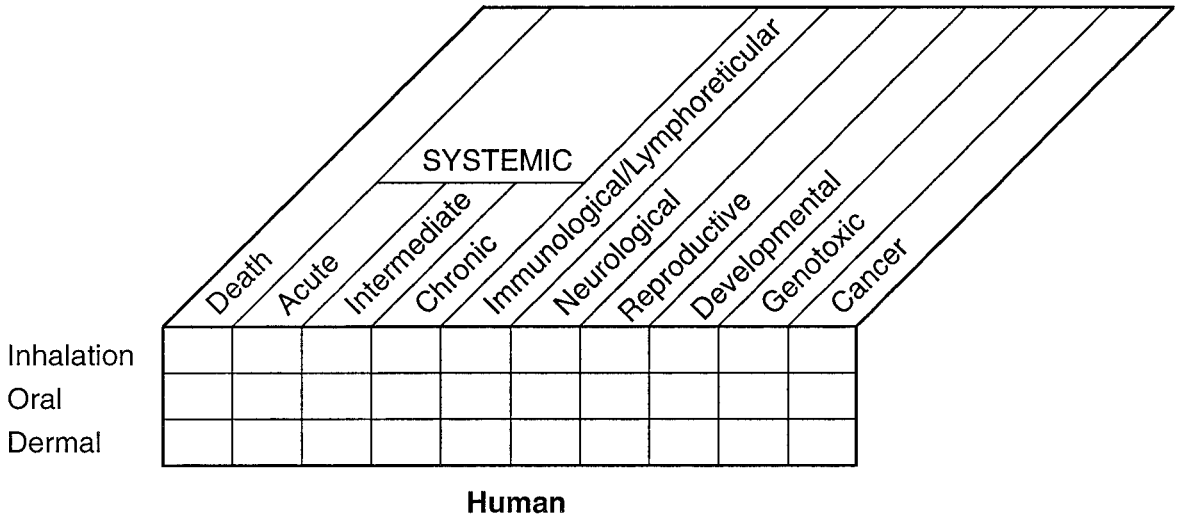
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to di-*n*-octylphthalate are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of di-*n*-octylphthalate. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989a), 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.

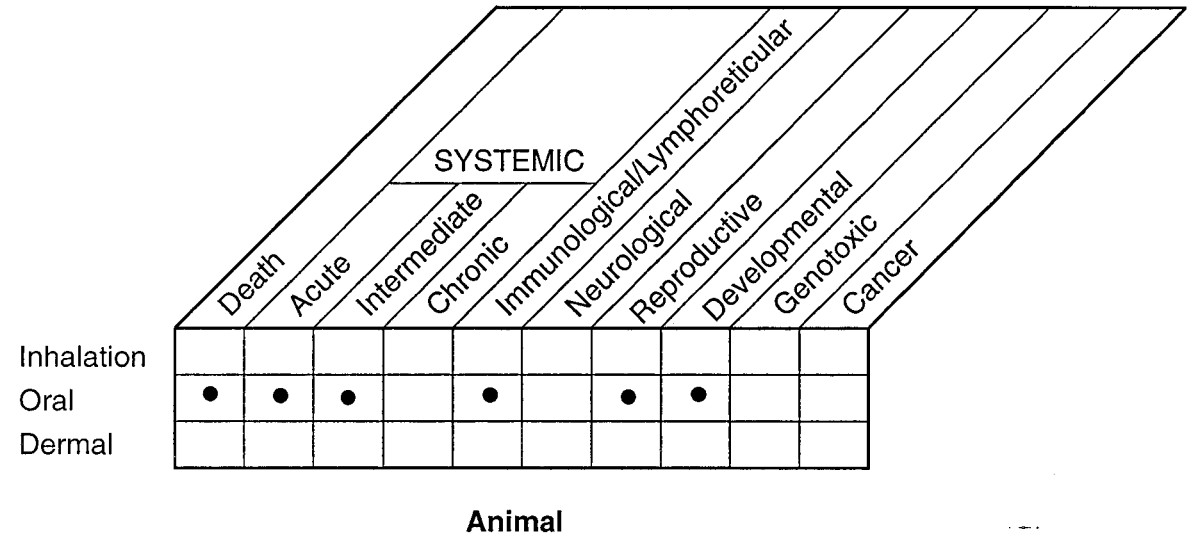
As can be seen in Figure 2-3, no information is available on the health effects of di-*n*-octylphthalate in humans, and very little information is available in animals. All of the available information on the toxicity of di-*n*-octylphthalate in animals comes from studies in which this compound was administered by either the oral or parenteral route; no information is available from animal studies on the toxicity of di-*n*-octylphthalate following inhalation or dermal exposure. Acute oral and parenteral lethality studies are available in animals, and the hepatic, immunological, reproductive, and developmental toxicity of di-*n*-octylphthalate has been studied following acute- and intermediate-duration parenteral and/or oral exposure in rats and mice. Among reliable studies, the longest duration found for di-*n*-octylphthalate exposure by any route is in a multigeneration reproductive toxicity oral gavage study (85-105 days) in mice and a promotion test dietary study (182 days) in rats.

2.10.2 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 di-*n*-octylphthalate. No information is available on the effects of acute-duration oral exposure to di-*n*-octylphthalate in humans. Therefore, the data are not sufficient to derive an acute inhalation MRL. An oral LD_{50} of di-*n*-octylphthalate of 53,700 mg/kg has been reported for male rats (Dogra et al. 1987). An oral LD_{50} of 13,000 mg/kg has been reported for mice (Dogra et al. 1989). LD_{50} values are also available for

FIGURE 2-3. Existing Information on Health Effects of Di-*n*-octylphthalate





● Existing Studies

intraperitoneal exposure (Dogra et al. 1985). The liver appears to be the target organ following acute-duration oral exposure to di-*n*-octylphthalate, and an acute oral MRL of 3 mg/kg/day was calculated based on increased relative liver weight and enzyme changes (Lake et al. 1986). Gross and microscopic changes in the liver were observed in rats fed di-*n*-octylphthalate for 10 days (Mann et al. 1985). Decreased thyroxine levels and ultrastructural changes in the thyroid were noted in rats fed di-n-octylphthalate in the diet (2,000 mg/kg/day) for 3 days in the Mann et al. (1985) study (Hinton et al. 1986).

The Mann et al. (1985) study is limited in that too few animals were used, organs other than the liver were not adequately evaluated, and only males were studied. Although an adequate acute-duration oral study would be useful to corroborate or refute the thyroid effects seen in the Mann et al. (1985) study, this does not represent a data need, since an acute oral MRL has been derived. Ingestion of contaminated drinking water is expected to be the predominant route of exposure for individuals living in the vicinity of hazardous waste sites. However, acute-duration inhalation and dermal studies in animals are needed to assess the potential toxicity of di-*n*-octylphthalate following exposure via these routes because there are insufficient pharmacokinetic data available to support the extrapolation of data obtained after oral administration to other routes of exposure.

Intermediate-Duration Exposure. There is no information available to identify target organs in humans or animals following intermediate-duration inhalation or dermal exposure to di-*n*-octylphthalate. Therefore, the data are not sufficient to derive an intermediate-duration inhalation MRL. No information is available on the effects of intermediate-duration oral exposure to di-*n*-octylphthalate in humans. The liver appears to be the target organ following intermediate-duration oral exposure to di-*n*-octylphthalate (DeAngelo et al. 1986; Mann et al. 1985; Poon et al. 1995). An intermediate-duration oral MRL of 0.4 mg/kg/day was calculated based on increases in hepatic ethoxyresorufin-*O*-deethylase activity and histopathological changes in the liver of rats (Poon et al. 1995). Mild microscopic changes were also noted in the thyroid in this study (Poon et al. 1995). Effects on the thyroid (decreased thyroxine levels, reduction in follicle size and colloid density, and ultrastructural changes) have been reported in rats fed diets containing di-*n*-octylphthalate for 21 days in the Mann et al. (1985) study (Hinton et al. 1986) or 13 weeks (Poon et al. 1995). Both the Mann et al. (1985) and the DeAngelo et al. (1986) studies are limited in that too few animals were used, organs other than the liver were not adequately evaluated, and only males were studied. Because statistical analysis was not performed on the data in the Poon et al. (1995) study and the thyroid

effects that were observed were mild, it is difficult to determine at which concentration the LOAEL for these particular effects occurred. Although ingestion of contaminated drinking water is expected to be the predominant route of exposure for individuals living in the vicinity of hazardous waste sites, intermediate-duration inhalation and dermal studies in animals are needed to assess the potential toxicity of di-*n*-octylphthalate following these routes of exposure because there are insufficient pharmacokinetic data available to support the extrapolation of data obtained after oral administration to other routes of exposure.

Chronic-Duration Exposure and Cancer. There is no information available to identify target organs in humans following chronic-duration inhalation, oral, or dermal exposure to di-*n*-octylphthalate. Therefore, the data are not sufficient to derive a chronic-duration inhalation MRL.
Chronic-duration oral toxicity studies using di-*n*-octylphthalate are needed to identify target organs and to establish the levels at which effects may occur. Oral studies are needed because ingestion of contaminated drinking water is expected to be the predominant route of exposure for individuals living in the vicinity of hazardous waste sites.

No studies were located regarding cancer in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate, and no studies were located in humans following oral exposure to this compound. Rats exposed to di-*n*-octylphthalate in the diet for either 10 or 26 weeks following a single subcarcinogenic intraperitoneal injection of diethylnitrosamine and partial hepatectomy exhibited increases in GGT-positive liver foci that were not associated with a peroxisome proliferation (Carter et al. 1992; DeAngelo et al. 1986). These results suggest that di-*n*-octylphthalate may be effective in promoting preneoplastic lesions in the rat liver, probably by a mechanism that does not rely on peroxisome proliferation. An oral cancer bioassay would be useful to establish whether di-n-octylphthalate has the potential to be carcinogenic to humans.

Genotoxicity. There is convincing evidence from microbial assays that di-*n*-octylphthalate is not a mutagen in *S. typhimurium* (Florin et al. 1980; Goodyear 1981a; Sato et al. 1994; Seed 1982; Shibamoto and Wei 1986; Zeiger et al. 1982, 1985) and does not induce DNA damage in *E. coli* (Goodyear 1981b). Although genetic toxicology testing, particularly in mammalian cell systems, is limited, the reported studies were well conducted and uniformly negative. It is, therefore, doubtful whether further investigation of these end points in other mammalian cell lines would alter the negative conclusions. Of greater importance, however, is the demonstrated lack of mutagenesis of the

rodent hepatocarcinogen, di(2-ethylhexyl)phthalate in a similar battery of *in vitro* tests. The inactivity of this carcinogenic phthalate suggests that *in vitro* genetic toxicology assays may have limited value for predicting the carcinogenic potential of other phthalates such as di-*n*-octylphthalate. Nevertheless, data from whole-animal studies using di-*n*-octylphthalate are needed since no literature exists on potential adverse genetic effects *in vivo*.

Reproductive Toxicity. No studies were located regarding reproductive effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate. No studies were located in humans following oral exposure to this compound. Di-*n*-octylphthalate caused significant decreases in human sperm motility *in vitro* (Fredricsson et al. 1993). The results of several acute- and intermediate-duration oral studies in rodents indicate that the potential of di-*n*-octylphthalate to cause adverse reproductive effects is low. Unlike other phthalate esters such as di(2-ethylhexyl)phthalate, di-n-octylphthalate does not appear to adversely affect testicular function or morphology (Foster et al. 1980; Gray and Butterworth 1980; Heindel et al. 1989; Morrissey et al. 1989; NTP 1985; Oishi 1990; Oishi and Hiraga 1980; Poon et al. 1995). However, some ultrastructural alterations in Leydig cells, including vesiculation of the smooth endoplasmic reticulum, were noted in rats administered di-*n*-octylphthalate by gavage on 2 consecutive days (Jones et al. 1993). Leydig cells obtained from rats that were cultured and stimulated by LH to measure cellular integrity by examining testosterone output showed decreased testosterone production when incubated with mono-*n*-octylphthalate, the major metabolite of di-*n*-octylphthalate (Jones et al. 1993). Examination of these cells exposed *in vitro* showed that mono-*n*-octylphthalate caused ultrastructural changes in several organelles, including the smooth endoplasmic reticulum dilatation and mitochondrial degeneration. No adverse effects on the female estrous cycle or on any index of reproductive function were seen in a multigeneration study in mice (Heindel et al. 1989; Morrissey et al. 1989; NTP 1985). Although it is fairly well established that di-*n*-octylphthalate does not induce adverse effects on male reproductive organs or reproductive performance in either males or females, data on reproductive organ pathology, including ultra-structural pathology, are needed in any 90-day studies that may be conducted with di-*n*-octylphthalate.

Developmental Toxicity. No studies were located regarding developmental effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate, and no studies were located in humans following oral exposure to this compound. The results of two oral studies in mice (one being a multigeneration reproductive toxicity study) indicate that di-*n*-octylphthalate has a very low potential to induce adverse developmental effects, especially in view of the very high doses that were evaluated

in these studies (Hardin et al. 1987; Heindel et al. 1989; Morrissey et al. 1989; NIOSH 1983; NTP 1985). No statistically significant and/or biologically significant effects were observed with respect either to embryo or fetal survival or growth, or to the incidence of skeletal or visceral malformations in offspring exposed *in utero*. However, a significant decrease in average fetal weight and a significantly increased incidence in gross fetal malformations were observed in the offspring of rats administered 4,890 mg/kg/day of di-*n*-octylphthalate by intraperitoneal injection (Singh et al. 1972). However, the effects seen following high-dose parenteral administration may not be relevant to human exposure. Well-conducted oral developmental toxicity studies in animals are needed to determine whether the negative results obtained in the two studies discussed above (one being a screen and the other being a multigeneration reproductive toxicity study not designed specifically to assess developmental toxicity) are valid, or if the effects seen after intraperitoneal administration of high doses of di-*n*-octylphthalate are likely to occur after oral administration. There are insufficient pharmacokinetic data available to support the extrapolation of data obtained after oral administration to other routes of exposure. However, oral studies would be the most useful since ingestion of contaminated drinking water is expected to be the predominant route of exposure for individuals living in the vicinity of hazardous waste sites.

Immunotoxicity. No studies were located regarding immunological effects in humans or animals following inhalation or dermal exposure to di-*n*-octylphthalate, or in humans following oral exposure to this compound. Limited data in rats or mice suggest that di-*n*-octylphthalate can exert immunotoxic effects following acute oral or parenteral exposure to relative high doses. These effects are reflected in changes in the weight and morphology of various lymphoreticular organs (thymus, spleen, and lymph nodes), altered activity of humoral antibody-forming cells and cellular mediators of immunity, and reduced resistance to bacterial, viral, protozoan, or other parasitic infection (Dogra et al. 1985, 1987, 1989). Additional data are needed to measure lymphoreticular organs and blood components of the immune system in any 90-day study that may be conducted with di-*n*-octylphthalate because the limited information available from animal studies suggests that this compound may exert immunotoxic effects.

Neurotoxicity. No information is available on the neurological effects of di-*n*-octylphthalate in humans or animals following inhalation or dermal exposure or in humans following oral exposure. No clinical signs of neurotoxicity were noted in acute and intermediate duration dietary exposure studies using mice (Heindel et al. 1989; NTP 1985). Although these data are limited, it is not believed that

the low-level exposure to di-*n*-octylphthalate that occurs at hazardous waste sites will result in neurotoxicity. Because there is no information to suggest that the central nervous system is a target of di-*n*-octylphthalate, no additional information is needed at this time.

Epidemiological and Human Dosimetry Studies. No epidemiological studies are available on populations that have been exposed solely to di-*n*-octylphthalate. As a result of its use, together with other phthalate esters, as a plasticizer in the production of polyvinyl chloride (PVC) resins and cellulose ester and polystyrene resins (EPA 1993a; HSDB 1995; Mannsville Chemical Products Corporation 1989) 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 di-*n*-octylphthalate and a control population with no known exposure could be identified. However, if suitable subpopulations could be found, then a well-conducted and controlled epidemiological study is needed to determine the potential target organs of di-*n*-octylphthalate toxicity in humans and the levels at which effects might be expected to occur. In addition, individuals at risk in the vicinity of hazardous waste sites could be identified and monitored.

Biomarkers of Exposure and Effect

Exposure. The monoester derivatives of di-*n*-octylphthalate and mono-*n*-octylphthalate or the oxidation products of mono-*n*-otylphthalates could potentially be used as a biomarker of exposure; however, only a few studies have been located that measure these metabolites in body tissues or fluids following exposure to di-*n*-octylphthalate (Albro and Moore 1974; Oishi 1990). Studies that investigate the fate and/or elimination of these metabolites are needed to determine its value as a biomarker of exposure for di-*n*-octylphthalate. Additional information on the metabolism of di-*n*-octylphthalate could help identify other potential biomarkers of exposure.

Effect. Since exposure to di-*n*-octylphthalate does not produce a unique clinical disease state, no biomarkers of effect have been identified. Additional information on the potential health effects of di-*n*-octylphthalate is needed to identify biomarkers of exposure to this compound.

Absorption, Distribution, Metabolism, and Excretion. No studies were located regarding the absorption of di-*n*-octylphthalate in humans and animals following inhalation and dermal exposure. Information on absorption in humans following oral exposure is not available. There are studies that suggest oral absorption of di-*n*-octylphthalate occurs in animals (Albro and Moore 1974; Oishi 1990; Poon et al. 1995); however, quantitative information is lacking. Additional information, primarily quantitative data, on absorption of di-*n*-octylphthalate for all routes of exposure is needed to understand and predict effects.

Information on the distribution of di-*n*-octylphthalate is limited to oral studies in rats, one by Oishi (1990), which reported the identification of mono-*n*-octylphthalate in blood and testes with peak levels observed at 3 hours for blood and at 6 hours for testes after dosing, and the other by Poon et al. (1995), which reported di-*n*-octylphthalate in the liver that was either below or slightly above detection limits; higher levels (15-25 ppm) of residue were also found in adipose tissue. However, this latter study was limited because metabolite levels were not measured. The metabolism of di-*n*-octylphthalate following acute exposure has been studied in animals *in vivo* and *in vitro* (Albro and Moore 1974; Brodsky et al. 1986; Lake et al. 1977). Metabolism studies following longer term exposures are needed in order to determine if metabolic pathways become saturated or altered. Although the Albro and Moore (1974) study seems to indicate that urine is the major elimination route of di-*n*-octylphthalate, additional excretion studies are needed to provide quantitative information. Additional studies on the mechanism involved in absorption and distribution of the compound are needed to provide information on how to increase elimination of the compound from the body.

Comparative Toxicokinetics. Based on the rat study by Albro and Moore (1974), di-*n*-octylphthalate appears to be readily absorbed following oral administration, metabolized extensively, and excreted primarily in the urine. Because of the lack of human data and limited animal data on the absorption, distribution, metabolism, and excretion of di-*n*-octylphthalate, additional studies are needed in order to make comparisons on the toxicokinetics across species.

Methods for Reducing Toxic Effects. All of the treatment methods currently available for use in di-*n*-octylphthalate ingestion or skin contact are supportive in nature and/or involve decreasing the absorption or increasing the rate of elimination of di-*n*-octylphthalate (Stutz and Ulin 1992). Since the mechanism of di-*n*-octylphthalate toxicity is not known, there are currently no methods that focus on mitigating the effects of di-*n*-octylphthalate by interfering with its mode of action. Therefore, more

information on the mechanism of action for di-*n*-octylphthalate is needed in order to devise methods for the mitigation of its toxic effects.

2.10.3 On-going Studies

No on-going studies on the health effects or toxicokinetics of di-*n*-octylphthalate were found.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

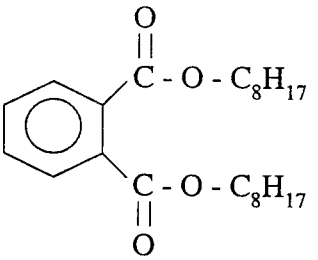
Information regarding the chemical identity of di-*n*-octylphthalate is located in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the chemical and physical properties of di-*n*-octylphthalate is located in Table 3-2.

There is conflicting information for many of these properties in the literature. A possible explanation for the inconsistencies, as discussed in Chapter 2, may come from the use of the nonspecific term "di-octylphthalate." This conflict has contributed to significant confusion and misinformation in the literature with respect to di-*n*-octylphthalate and the much more common isomer, di(2-ethylhexyl)phthalate. Although frequently being interpreted as referring to di-*n*-octylphthalate, it is apparent that in almost all cases "di-octylphthalate" and "DOP" have in fact been used as synonyms for di(2-ethylhexyl)phthalate. Therefore, many of the properties found for di-*n*-octylphthalate or di-octylphthalate may possibly be for di(2-ethylhexyl)phthalate.

TABLE 3-1. Chemical Identity of Di-*n*-octylphthalate

Characteristic	Information	Reference
Chemical name	Di-*n*-octylphthalate	HSDB 1995
Synonym(s)	1,2-benzenedicarboxylic acid, di-*n*-octyl ester; 1,2-benzene-dicarboxylic acid, dioctyl ester; *o*-benzenedicarboxylic acid, dioctyl ester; DNOP; DOP; dioctyl 1,2-benzene-dicarboxylate; dioctyl *o*-benzenedicarboxylate; octyl phthalate; dioctyl phthalate; *n*-octyl phthalate; phthalic acid, dioctyl ester	HSDB 1995; EPA 1987a
Registered trade name(s)	Celluflux DOP; Dinopol NOP; Polycizer 162; PX-138; Vinicizer 85	HSDB 1995
Chemical formula	$C_{24}H_{38}O_4$	HSDB 1995
Chemical structure		EPA 1987a
Identification numbers:		
CAS registry	117-84-0	HSDB 1995
NIOSH RTECS	TI 1925000	HSDB 1995
EPA hazardous waste	U 107	HSDB 1995
OHM/TADS	8300217	HSDB 1995
DOT/UN/NA/IMCO shipping	No data	
HSDB	1345	IRIS 1995
NCI	No data	

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous 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 Di-*n*-octylphthalate

Property	Information	Reference
Molecular weight	390.54	Clayton and Clayton 1981
	390.56	HSDB 1995
	390.57	EPA 1987b
	390.62	EPA 1987a; Sax and Lewis 1989; NIOSH RTECS 1987
Color	Colorless	EPA 1987a
Physical state	Liquid	EPA 1987a
Melting point	-25°C	EPA 1987a
Boiling point		
at 760 mm Hg	390–420°C	EPA 1993a
at 5 mm Hg	230°C	Sittig 1991
at 4 mm Hg	220–240°C	EPA 1987a
	220°C	HSDB 1995
Density:		
at 25°C	0.978 g/mL	HSDB 1995
Odor	Odorless	EPA 1993
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 25°C	0.2 mg/L	EPA 1992a
	3.0 mg/L	Wolfe et al. 1980; HSDB 1995
Organic solvent(s)	Soluble	EPA 1987a
Partition coefficients:		
Log K_{ow}	5.22	EPA 1987a; HSDB 1995
Log K_{oc}	4.28	Wolfe et al. 1980
Vapor pressure at 25°C	1.44×10^{-4} mm Hg	EPA 1987a
Henry's law constant	5.5×10^{-6} H atm-m^3/mole	EPA 1992a
	6.68×10^{-5} H atm-m^3/mole	EPA 1992a
Autoignition temperature	No data	
Flashpoint	219°C	Sittig 1991
Flammability limits	No data	
Conversion factors	No data	
Explosive limits	No data	

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Di-*n*-octylphthalate is produced commercially as a component of mixed phthalate esters, including straight- chain C6, C8, and Cl0 phthalates (EPA 1993a). Di-*n*-octylphthalate is produced at atmospheric pressure or in a vacuum by heating an excess of n-octanol with phthalic anhydride in the presence of an esterification catalyst such as sulfuric acid or p-toluenesulfonic acid. The process may be either continuous or discontinuous (EPA 1993a; HSDB 1995). Di-*n*-octylphthalate can also be produced by the reaction of n-octylbromide with phthalic anhydride.

The most recent report available on di-*n*-octylphthalate lists three commercial producers: Vista Chemical Company, Houston, Texas; Aristech Chemical Corporation, Neville Island, Pennsylvania; and Teknor Apex Company, Hebronville, Massachusetts and Brownsville, Texas (EPA 1993a). Additional reported producers include: Eastman Kodak Company, Rochester, New York (USITC 1994); Tenneco Chemical, Inc., Chestertown, Maryland (EPA 1987a); Alfa Products, Morton Thiokol, Inc., Danvers, Massachusetts; Primachem, Inc., Englewood Cliffs, New Jersey; and GCA Chemical Corp., Stamford, Connecticut (HSDB 1995). Table 4-1 lists the U.S. facilities that manufacture or process di-*n*-octylphthalate.

The current annual production of di-*n*-octylphthalate is difficult to estimate because of confusion in nomenclature regarding the octylphthalate isomers and reported data describing only the entire group of dioctyl orthophthalates. A total of 122,384 metric tons of total dioctylphthalates were produced in 1992 (USITC 1994). The amount of di-*n*-octylphthalate included in this group was not reported because of the possible revelation of confidential business information.

Table 4-l lists data from the Toxics Release Inventory (TRI) regarding U.S. companies that reported the manufacture and use of di-*n*-octylphthalate in 1992 (TR192 1994). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Table 4-1. Facilities That Manufacture or Process Di-n-octylphthalate

Facility	Location[a]	Range of maximum amounts on site in pounds	Activities and uses
NA	AL	10,000-99,999	As a formulation component
HALSTEAD IND. INC.	AR	10,000-99,999	As a formulation component
GILLETTE CO.	CA	1,000-9,999	As a formulation component
NA	GA	10,000-99,999	Import; For sale/distribution; As a formulation component
NA	IL	1,000-9,999	As a formulation component
NA	IL	1,000-9,999	As a formulation component
NEW EXTRUSTIONS & FABRICATING	IL	10,000-99,999	As a formulation component; As a chemical processing aid; Ancillary uses
EASTERN INDUSTRIES	IL	10,000-99,999	As a product component
DOW CHEMICAL CO.	IL	10,000-99,999	As a formulation component
BRC RUBBER GROUP INC.	IN	10,000-99,999	As a formulation component
ATOCHEM N.A. INC.	KY	10,000-99,999	As a formulation component; As a chemical processing aid
VISTA CHEMICAL CO.	MA	10,000-99,999	As a formulation component
LEVITON MFG.	MA	100,000-999,999	As a product component
BRADFORD IND. INC.	MA	1,000-9,999	As a formulation component
NA	MA	1,000-9,999	As a formulation component
O'SULLIVAN CORP.	MA	10,000-99,999	As a formulation component
AMERICAN CYANAMID CO.	MI	100-999	Ancillary uses
GENERAL CABLE IND. INC.	MI	10,000-99,999	As a formulation component; As a product component
NA	MO	1,000-9,999	In repackaging only
GOODYEAR TIRE & RUBBER CO.	MO	10,000-99,999	As a reactant; As a formulation component
VISTA CHEMICAL CO.	MS	100,000-999,999	Produce; For on-site use/processing; For sale/distribution; As a formulation component
HALSTEAD IND. INC.	NC	10,000-99,999	As a formulation component
NA	NC	1,000-9,999	As a formulation component
UNIROYAL CHEMICAL CO. INC.	NC	10,000-99,999	As a formulation component

Table 4-1. Facilities That Manufacture or Process Di-n-octylphthalate (continued)

Facility	Location[a]	Range of maximum amounts on site in pounds	Activities and uses
KONICA CORP.	NC	1,000-9,999	Ancillary uses
HBD INDUSTRIES INC.	NC	10,000-99,999	Import; For on-site use/processing; As a formulation component; As a chemical processing aid
PLASTICS SPECIALTIES & TECHNOL	NJ	100,000-999,999	As a formulation component
OCCIDENTAL PETROLEUM CORP.	NJ	10,000-99,999	As a formulation component
PLASTIC SPECIALTIES & TECHNOLO	NJ	10,000-99,999	As a formulation component
NA	NJ	10,000-99,999	As a formulation component
NA	NJ	1,000-9,999	As a formulation component
PLASTICS SPECIALTIES & TECHNOL	NV	10,000-99,999	As a formulation component
HM HOLDINGS INC.	NY	1,000-9,999	As a formulation component
NA	NY	10,000-99,999	As a product component
GOODYEAR TIRE & RUBBER CO.	OH	1,000-9,999	As a formulation component; As a product component; Ancillary uses
COOKSON AMERICA	OH	10,000-99,999	As a formulation component
BORDEN INC.	OH	10,000-99,999	As a product component
NA	OH	100-999	Import; For on-site use/processing; As a formulation component
A. SCHULMAN INC.	OH	10,000-99,999	As a formulation component
NA	OH	1,000-9,999	As a product component
ACC MIDDLE CORP.	PA	100,000-999,999	Produce; For sale/distribution
NA	PA	10,000-99,999	As a formulation component
NA	TN	100-999	As a formulation component
NA	TN	10,000-99,999	As a product component
GMC	TN	100,000-999,999	As a product component
NA	TN	10,000-99,999	As a formulation component
TEXAS IND. INC.	TX	1,000-9,999	Ancillary uses

Table 4-1. Facilities That Manufacture or Process Di-n-octylphthalate (continued)

Facility	Location[a]	Range of maximum amounts on site in pounds	Activities and uses
TANDY CORP.	TX	1,000-9,999	As a formulation component
AMERON INC.	TX	10,000-99,999	As a reactant; As a formulation component
NA	UT	10,000-99,999	As a formulation component
NA	VA	1,000-9,999	As a formulation component
NA	VA	100,000-999,999	As a formulation component
UNIROYAL TECH. CORP.	WI	10,000-99,999	As a formulation component
NA	WI	10,000-99,999	As a formulation component
NA	WV	10,000-99,999	As a formulation component

Source: TRI92 1994

[a] Post office state abbreviations used

NA = not available

4.2 IMPORT/EXPORT

In 1988, 6 million pounds of di-octylphthalates (i.e., di-*n*-octylphthalate and di[2-ethylhexyl]phthalate) were imported and 37 million pounds were exported. No data were located on specific quantities for di-*n*-octylphthalate (Mannsville Chemical Products Corporation 1989).

4.3 USE

Di-*n*-octylphthalate is principally used as a plasticizer in the production of plastics (Sittig 1991) and PVC resins. When used as a plasticizer, di-*n*-octylphthalate can represent 5-60% of the total weight of the plastics and resins. It increases flexibility and enhances or alters the properties of the material. It is also used for cellulose ester and polystyrene resins, as a dye carrier in plastic production (primarily PVC), and as a chemical intermediate in the manufacture of adhesives, plastisols, and nitrocellulose lacquer coatings (EPA 1993a; HSDB 1995; Mannsville Chemical Products Corporation 1989). It is a registered active ingredient in pesticides (EPA 1987b) and is found in cosmetics and colorants (EPA 1992a). Di-*n*-octylphthalate also serves as a carrier for catalysts or initiators and as a substitute for electrical capacitor fluid (EPA 1992a).

Flexible PVC resins and other dioctylphthalate-containing plastics and resins are used in a variety of industrial and domestic products: plastisols for carpetback coating (EPA 1987b), film, wire, cables, and adhesives (HSDB 1995). Additional end-use products are automobile and furniture upholstery, wall coverings, window shades, garden hoses, shower curtains, tablecloths, rainwear, shoes, dolls, and toys (Mannsville Chemical Products Corporation 1989).

4.4 DISPOSAL

Di-*n*-octylphthalate, including waste containing di-*n*-octylphthalate, is classified as a hazardous waste product by EPA. Generators of waste containing this contaminant must conform to EPA regulations for treatment, storage, and disposal (see Chapter 7). Rotary kiln or fluidized bed incineration methods are acceptable disposal methods for these wastes. Liquid injection incineration may also be used (HSDB 1995).

According to the TRI, 240,609 pounds of di-*n*-octylphthalate were transferred to landfills and/or treatment/disposal facilities in 1992 (see Section 5.2) (TR192 1994). Of this quantity, about 1,475 pounds were discharged to publicly owned treatment works. A total of 15,302 pounds was released to air, land, and water by manufacturing and processing facilities. No di-*n*-octylphthalate was released for underground injection.

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Di-*n*-octylphthalate is released mainly to the atmosphere and to some extent to surface waters in industrial effluents (TRI92 1994). The compound may be released to soils in the disposal of plastics wastes. Di-*n*-octylphthalate is expected to partition mainly to soils and sediment upon release to the environment (EPA 1979, 1992c). The compound is also bioconcentrated by aquatic organisms, although biomagnification in aquatic food chains is not expected to be significant (EPA 1992d). Aerobic biodegradation is the most important transformation process in soils and surface waters (EPA 1992a, 1992c). Other transformation processes include photooxidation in the atmosphere and photolysis in surface waters (EPA 1992a). As a result of confusion with its branched isomer, di(2-ethylhexyl)phthalate, limited unambiguous monitoring data are available for di-*n*-octylphthalate. The compound has been detected in ambient air, rain, runoff, groundwater, surface water, and sediment.

Human exposure to the compound is expected to occur primarily in workplace settings (HSDB 1995). General population exposure pathways include inhalation of the volatilized plasticizer, ingestion of foods contaminated as a result of leaching of di-*n*-octylphthalate from plastic containers, ingestion of aquatic organisms that have bioconcentrated the compound, and ingestion of contaminated drinking water (EPA 1992c). Populations living near hazardous waste sites contaminated with di-n-octylphthalate may also be exposed through dermal contact with and ingestion of contaminated groundwater and sediments (ATSDR 1988, 1989b, 1989c). Populations with potentially high exposures to di-*n*-octylphthalate include workers in the chemical manufacturing and plastics manufacturing and processing industries, individuals requiring routine medical care, such as blood transfusions and kidney dialysis treatments, and individuals living in the vicinity of industrial manufacturing and processing facilities that may manufacture or use di-*n*-octylphthalate or of hazardous waste sites containing di-*n*-octylphthalate or plastics (HSDB 1995).

Di-*n*-octylphthalate has been identified in at least 300 of the 1,416 hazardous waste sites on the EPA National Priorities List (NPL) (HazDat 1995). However, the number of sites evaluated for di-n-octylphthalate is not known. The frequency of these sites within the United States can be seen in

Figure 5-1. Of these sites, 298 are located in the United States and 2 are located in the Commonwealth of Puerto Rico (not shown).

5.2 RELEASES TO THE ENVIRONMENT

Considerable confusion exists in the literature about the TRI release reporting data and monitoring data available for di-*n*-octylphthalate and its more common branched isomer, di(2-ethylhexyl)phthalate (EPA 1992a; Vista Chemical 1992). The confusion exists because the terms "dioctyl phthalate" and "DOP" are often used as synonyms for di(2-ethylhexyl)phthalate, which is the largest volume plasticizer used in PVC. Consequently, some of the historical release and monitoring data reported in the literature as "dioctyl phthalate" and "DOP" refer to the more common branched isomer rather than di-*n*-octylphthalate. Therefore, releases of di-*n*-octylphthalate and concentrations of the compound in ambient media may actually be lower than historical data suggest. Di-*n*-octylphthalate was withdrawn from the TRI effective in 1993 (EPA 1995h). Thus, the data for TRI92 (1994) is the most recent data that is available from the Toxic Release Inventory for di-*n*-octylphthalate.

5.2.1 Air

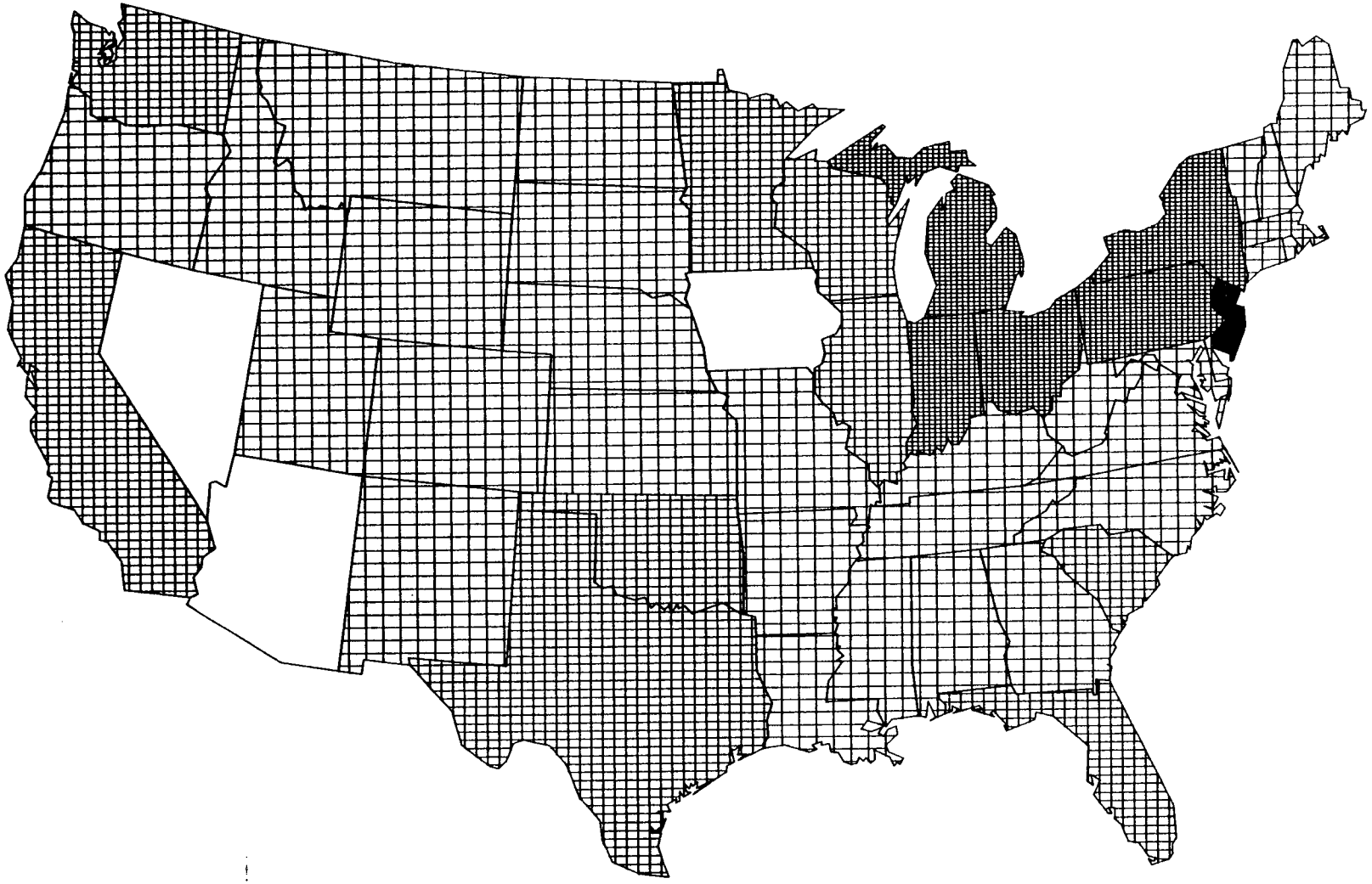
Di-*n*-octylphthalate may be released to the atmosphere through volatilization of the compound from plastics, as a result of manufacturing processes, and through incineration (Vista Chemical 1992).

According to TR192 (1994), an estimated total of 15,011 pounds of di-*n*-octylphthalate, amounting to about 98% of the total environmental release, were discharged to the atmosphere from manufacturing and processing facilities in the United States in 1992 (see Table 5-l). The TRI data listed in Table 5-l should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Furthermore, as noted above, the precise chemical identity of the reported releases is questionable.

5.2.2 Water

Di-*n*-octylphthalate is released to surface waters in industrial waste waters from production and use processes and as a result of spills during its transport, storage, and use (Mathur 1974a). For example, di-*n*-octylphthalate was found in one of five industrial process waste waters sampled at an average

FIGURE 5-1. FREQUENCY OF NPL SITES WITH DI-N-OCTYL PHTHALATE CONTAMINATION *



*Derived from HazDat 1995

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Di-n-octylphthalate

State[a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment[b]	POTW transfer	Off-site waste transfer
AL	NA	NA	250				250		
AR	NA	HALSTEAD IND. INC.							195
CA	NA	GILLETTE CO.							
GA	NA	NA	10		250		260	250	250
IL	NA	NA	1,500				1,500		2
IL	NA	NA							
IL	NA	NEW EXTRUSTIONS & FABRICATING							
IL	NA	EASTERN INDUSTRIES	11				11		
IL	NA	DOW CHEMICAL CO.	206				206		
IN	NA	BRC RUBBER GROUP INC.							
KY	NA	ATOCHEM N.A. INC.	30				30		
MA	NA	VISTA CHEMICAL CO.	3,110	5			3,115		260
MA	NA	LEVITON MFG.							32,844
MA	NA	BRADFORD IND. INC.	23				23		80
MA	NA	NA	635				635		2,731
MA	NA	O'SULLIVAN CORP.	500				500		1
MI	NA	AMERICAN CYANAMID CO.	255				255	250	
MI	NA	GENERAL CABLE IND. INC.							7,307
MO	NA	NA							
MO	NA	GOODYEAR TIRE & RUBBER CO.	500				500	5	
MS	NA	VISTA CHEMICAL CO.		30			30		13,895
NC	NA	HALSTEAD IND. INC.							

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Di-n-octylphthalate (continued)

State[a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment[b]	POTW transfer	Off-site waste transfer
NC	NA	NA							
NC	NA	UNIROYAL CHEMICAL CO. INC.	500				500		250
NC	NA	KONICA CORP.						250	5,500
NC	NA	HBD INDUSTRIES INC.						250	5
NJ	NA	PLASTICS SPECIALTIES & TECHNOL							88
NJ	NA	OCCIDENTAL PETROLEUM CORP.							16
NJ	NA	PLASTIC SPECIALTIES & TECHNOLO							
NJ	NA	NA	140				140		
NJ	NA	NA							
NV	NA	PLASTICS SPECIALTIES & TECHNOL							
NY	NA	HM HOLDINGS INC.	94				94		6,900
NY	NA	NA							9,869
OH	NA	GOODYEAR TIRE & RUBBER CO.							
OH	NA	COOKSON AMERICA	500				500	5	1,741
OH	NA	BORDEN INC.	3,300				3,300		35,260
OH	NA	NA							53
OH	NA	A. SCHULMAN INC.	1,700				1,700	5	10,700
OH	NA	NA	91				91		
PA	NA	ACC MIDDLE CORP.	392				392	460	170
PA	NA	NA	250				250		
TN	NA	NA	5				5		

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Di-n-octylphthalate (continued)

State[a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment[b]	POTW transfer	Off-site waste transfer
TN	NA	NA	5	5			10		
TN	NA	GMC							12,699
TN	NA	NA							12,061
TX	NA	TEXAS IND. INC.							
TX	NA	TANDY CORP.							2,597
TX	NA	AMERON INC.	140				140		
UT	NA	NA							
VA	NA	NA	500				500		
VA	NA	NA	255				255		13,659
WI	NA	UNIROYAL TECH. CORP.	103				103		70,001
WI	NA	NA	5				5		
WV	NA	NA	1	1			2		
		Totals	15,011	41	250		15,302	1,475	239,134

Source: TRI92 1994

[a] Post office state abbreviations used
[b] The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

NA = not available; POTW = publicly owned treatment works

concentration of 3,700 µg/L (EPA 1981). Releases to surface waters are expected to undergo secondary treatment at publicly owned treatment works or at on-site National Pollutant Discharge Elimination System (NPDES) permitted facilities. Such waste-water treatment systems are expected to remove 80-90% of the influent di-*n*-octylphthalate through a combination of adsorption and aerobic biodegradation by acclimated microorganisms (EPA 1992c Petrasek et al. 1983). The compound is also released to surface waters from nonpoint sources, such as surface runoff. For example, di-n-octylphthalate was found in runoff samples collected in 1982 from Little Rock, Arkansas, Bellevue, Washington, and Eugene, Oregon, at a 4% frequency of detection in the collected samples and at concentrations of 0.4-l µg/L. This sampling was conducted as part of the Nationwide Urban Runoff Program (Cole et al. 1984).

According to TR192 (1994), an estimated total of 41 pounds of di-*n*-octylphthalate were discharged to surface waters from manufacturing and processing facilities in the United States in 1992 (see Table 5-l). An estimated total additional 1,475 pounds were transferred to publicly owned treatment works. The TRI data listed in Table 5-l should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Furthermore, as noted above, the precise chemical identity of the reported releases is questionable.

5.2.3 Soil

According to TR192 (1994), an estimated total of 250 pounds of di-*n*-octylphthalate, amounting to about 2% of the total environmental release, was discharged to soils from manufacturing and processing facilities in the United States in 1992 (see Table 5-l). An estimated total additional 239,134 pounds were transferred to off-site waste treatment, storage, and disposal facilities. The TRI data listed in Table 5-l should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Furthermore, as noted above, the precise chemical identity of the reported releases is questionable.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Upon release to surface waters, di-*n*-octylphthalate is expected to partition mainly to sediments and to suspended particulates. In a pilot-scale waste-water treatment system, di-*n*-octylphthalate partitioned mainly to primary treatment sludge (Petrasek et al. 1983). The compound strongly adsorbs to organic matter contained in soils and sediments; adsorption is probably the most important transport process for the compound in surface waters (EPA 1979, 1992c). Volatilization from surface waters is expected to be a slow and unimportant process. For example, the estimated volatilization half-life from a model river 1 meter deep with a current of 1 meter/second and a wind speed of 3 meters/second is 13 days (HSDB 1995). In a pilot-scale study of a typical waste-water treatment plant employing both primary and secondary activated sludge treatment processes, no di-*n*-octylphthalate was lost from the system by air stripping (Petrasek et al. 1983). However, in a study simulating the behavior of di-*n*-octylphthalate in different aquatic systems, volatilization was estimated to account for up to 20% of the losses of the compound from certain standing surface water systems characterized by long water detention times (e.g., ponds, lakes), especially in relatively pristine lakes where loss by biodegradation is not likely to be important (Wolfe et al. 1980). This same study suggests that in running surface waters, such as rivers, di-*n*-octylphthalate is most likely to be lost by transport out of the system.

Di-*n*-octylphthalate also strongly adsorbs to soils and does not undergo leaching to groundwater, as indicated by its estimated soil organic carbon/water partition coefficient (K_{oc}) of about 19,000. Volatilization from soils is not expected to be significant (HSDB 1994; Vista Chemical 1992).

Di-*n*-octylphthalate released to the atmosphere may partition to soils and surface waters through wet (Ligocki et al. 1985) and dry (Vista Chemical 1992) deposition processes.

Di-*n*-octylphthalate is bioconcentrated by aquatic organisms (EPA 1992d). In a 33-day combined terrestrial-aquatic model ecosystem study, the following di-*n*-octylphthalate bioconcentration factors (BCFs) were reported: (1) algae - 28,500; (2) daphnids - 2,600; (3) fish and mosquitoes - 9,400; and (4) snails - 13,600. However, the half-life for the disappearance of di-*n*-octylphthalate from this model system was estimated to be about 5 days as the result of metabolism of the compound. An EPA (1992d) hazard assessment stated that although di-*n*-octylphthalate does bioconcentrate in aquatic

organisms, the compound is not expected to biomagnify in aquatic food chains; however, this citation did not contain, and does not reference any studies that provide, a basis for this conclusion. In greenhouse studies using radiolabeled di-*n*-octylphthalate added to soils, the compound was not bioconcentrated by crop plants (BCF <1) (EPA 1986e). In a more recent screening study that examined the potential of contaminants contained in sewage sludge to transfer into agricultural products on the basis of their physical/chemical properties, di-*n*-octylphthalate was judged to have a high potential to adsorb to soil, sludge solids, and plant root surfaces, and a low potential for leaching, uptake and translocation by plants, and transfer to animal tissues by foliage ingestion (Wild and Jones 1992).

5.3.2 Transformation and Degradation

5.3.2.1 Air

The most important transformation process for di-*n*-octylphthalate present in the atmosphere as an aerosol is reaction with photochemically produced hydroxyl radicals. The half-life for this reaction has been estimated to be 4.5-44.8 hours (Howard et al. 1991). Actual atmospheric half-lives may be longer since phthalate esters sorbed to wind-entrained particulates may have long atmospheric residence times (Vista Chemical 1992). Direct photolysis in the atmosphere is not expected to be an important process (EPA 1993a; HSDB 1995).

5.3.2.2 Water

Phthalate esters undergo a step-wise alkaline hydrolysis to monoesters and then to dicarboxylic acids. As a result of the relatively slow rates of this reaction at pH 6-9 and the low water solubility of di-n-octylphthalate, chemical hydrolysis of the compound is not an environmentally important transformation process (EPA 1992a). Hydrolytic half-lives at 25°C and pH 7 and 9 have been estimated to be 107 and 7 years, respectively (Howard et al. 1991).

Biodegradation is the primary process by which phthalate esters are removed from surface waters; rates are strongly dependent on acclimation of microbial communities (EPA 1992a, 1992~). Wolfe et al. (1980) predicted that biodegradation would be the most important mechanism by which di-n-octylphthalate would be removed from eutrophic lakes. In static culture flask biodegradation screening

tests, about 93-94% of di-*n*-octylphthalate was metabolized after 3 weeks only after serial subculturing of acclimated microorganisms (Tabak et al. 1981). Enzymatic hydrolysis is the mechanism used by microbes in the aerobic biotransformation of di-*n*-octylphthalate. The ester is hydrolyzed to soluble intermediates, presumably via a pathway producing a phthalic acid monoester (EPA 1993a); however, data on the identity of biodegradation products were not available. Aerobic biodegradation half-lives range from 1 to 4 weeks in surface waters and from 2 weeks to 1 year in groundwater (Howard et al. 1991). Biodegradation under anaerobic conditions occurs at a slower rate (EPA 1993a); it has been predicted that di-*n*-octylphthalate will accumulate in natural sediments because it is persistent under anaerobic conditions (EPA 1992d). For example, in anaerobic digester studies using diluted and undiluted sewage treatment plant sludge, between 40% and 75% of di-*n*-octylphthalate remained undegraded after a 10-week incubation period (Shelton et al. 1984). Anaerobic half-lives for aquatic systems have been predicted to range from 6 months to 1 year (Howard et al. 1991).

Di-*n*-octylphthalate may also undergo photolysis in surface waters as a result of its absorption of electromagnetic radiation at wavelengths less than 290 nm. The estimated photolytic half-life of the compound in surface water is 144 days (EPA 1992a). Photolysis was predicted to be the most important removal mechanism after volatilization for di-*n*-octylphthalate losses from oligotrophic lakes (Wolfe et al. 1980).

5.3.2.3 Sediment and Soil

As discussed above, aerobic biotransformation is expected to be the most important process in the removal of di-*n*-octylphthalate from soils; anaerobic biodegradation occurs in sediments (EPA 1992a). However, because of its persistence under anaerobic conditions, di-*n*-octylphthalate is expected to accumulate in sediments (EPA 1992d). Di-*n*-octylphthalate has been reported to undergo biodegradation by a variety of acclimated soil microorganisms (HSDB 1995; Mathur 1974b); however, data on the identity of biodegradation products were not located.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

As previously discussed, considerable confusion exists in the literature about the monitoring data available for di-*n*-octylphthalate and di(2-ethylhexyl)phthalate. Only monitoring data that clearly

concerned di-*n*-octylphthalate were included in this section of the profile; data from ambiguous studies were not included.

5.4.1 Air

Di-*n*-octylphthalate was detected in five of seven ambient air and six of seven rainwater samples collected during rain events that occurred in February through April 1984 in Portland, Oregon. Di-n-octylphthalate concentrations ranged from 2.6 to 20 ng/L in rain samples and from 0.06 to 0.94 ng/m^3 in air samples (Ligocki et al 1985).

5.4.2 Water

Di-*n*-octylphthalate was detected in 4% of the urban runoff samples collected from a total of 15 cities. Di-*n*-octylphthalate was detected at three cities at concentrations of 0.4-l µg/L (Cole et al. 1984). The compound was found in water samples collected at four locations along the entire length of the Mississippi River at concentrations of 24-310 ng/L (DeLeon et al. 1986). At the Butler Mine Tunnel NPL Site located in Pittston, Pennsylvania, di-*n*-octylphthalate was detected in on-site oil/groundwater samples at concentrations of ll0-792,000 ppb (ATSDR 1989b). Di-*n*-octylphthalate was detected at a concentration of 1 ppb in a water sample collected from the discharge pond of a phthalate ester plant located on the Chester River in Maryland (Peterson and Freeman 1984). Di-*n*-octylphthalate was found at 0.001-0.02 ppm in water samples taken from a river that received industrial waste water from a specialty chemical manufacturing plant (Jungclaus et al. 1978).

Estimates of di-*n*-octylphthalate concentrations in receiving waters located downstream from two plants reporting releases of the compound to the TRI have been developed by EPA (1992c). Mean flow concentrations of about 3-9 µg/L and 7-year Ql0 low-flow concentrations of about 90-390 µg/L were estimated for the surface waters receiving effluent from the on-site treatment facility used at one plant and the publicly owned treatment facility that handles the effluent from the other plant.

Concentrations of di-*n*-octylphthalate in drinking water utility influents have been estimated to be less than 0.5 ppb (EPA 1992c).

5.4.3 Sediment and Soil

In the sediment of a discharge pond of a phthalate ester plant located on the Chester River in Maryland, di-*n*-octylphthalate was detected at a concentration of 12,000 ppb. In sediment samples from the Chester River taken 2 km and 8 km downstream from the plant, the compound was found at concentrations of 62 and <5 ppb, respectively (Peterson and Freeman 1984). In the sediment of a river that received industrial waste water from a specialty chemical manufacturing plant, di-n-octylphthalate was detected at concentrations ranging from 1.5 to 25 ppm (Jungclaus et al. 1978). At the Dixie Caverns Landfill NPL site located in Salem, Virginia, di-*n*-octylphthalate was detected on-site at a concentration of 80 ppm (ATSDR 1988); however, the media in which this concentration was detected was not specified. Off-site sediment samples collected at the Revere Chemical Company NPL site located in Revere, Pennsylvania, were found to contain 2,300 ppb di-*n*-octylphthalate (ATSDR 1989c).

EPA (1992c) developed estimates of di-*n*-octylphthalate concentrations in the sediments of surface waters located downstream from two plants reporting releases of the compound to the TRI. The surface waters received effluents from an on-site treatment facility and a publicly owned treatment facility. Steady-state sediment concentrations were estimated to exceed 10 mg/kg and possibly >50 mg/kg downstream from the two facilities.

5.4.4 Other Environmental Media

Di-*n*-octylphthalate is produced as a decomposition product of the pesticide dinocap (HSDB 1995).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Humans are expected to be exposed to di-*n*-octylphthalate mainly in the workplace (HSDB 1994). The National Occupational Exposure Survey (NOES), conducted between 1981 and 1983; estimated that 10,393 workers (including 1,434 women) in 1,177 facilities were exposed to di-*n*-octylphthalate in the workplace in 1980 (NIOSH 1993).

Exposure of the general population to di-*n*-octylphthalate may occur through ingestion of foods contaminated by leaching of the compound from plastic containers, transfusions of blood or other

fluids through medical tubing, ingestion of aquatic organisms that have bioconcentrated the compound, and consumption of contaminated drinking water (EPA 1992c; HSDB 1995). An additional potential source of human exposure is contact with contaminated media at hazardous waste sites. For example, di-*n*-octylphthalate has been detected in on-site sediment and groundwater samples and off-site sediment samples collected at NPL hazardous waste sites. The human exposure pathways of concern at these sites include ingestion of contaminated groundwater and sediment (ATSDR 1988, 1989b, 1989c). Since data are not available on the dermal absorption of di-*n*-octylphthalate, it is not known whether dermal contact with di-*n*-octylphthalate at hazardous waste sites would represent an exposure pathway of concern.

In an early report of the 1982 annual results of the National Human Adipose Tissue Survey (NHATS), a compound identified as di-*n*-octylphthalate was reportedly detected in 31% of the composite human adipose tissue samples taken in the various regions of the United States that year. Concentrations in lipid ranged from below the level of detection (9 ng/sample) to a maximum of 850 ng/g (EPA 1986d). However, a later report of the 1982 results stated that the chemical detected was not di-n-octylphthalate, but was actually diethylhexyl phthalate (EPA 1989b).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Patients receiving regular dialysis on a kidney machine or receiving blood transfusions may be the populations with the highest potential exposure to di-*n*-octylphthalate. Workers in industries that produce or use plastics, especially materials processed at high temperatures, are also expected to have potentially high exposure to di-*n*-octylphthalate especially via inhalation of the volatilized plasticizer. Members of the general population living in the vicinity of industrial facilities that manufacture or process the compound or plastic materials containing the compound, as well as individuals living near hazardous waste sites known to be contaminated with di-*n*-octylphthalate, are also expected to have potentially high exposures through contact with contaminated environmental media (HSDB 1995).

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 di-*n*-octylphthalate is available. Where adequate

information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of di-*n*-octylphthalate.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of di-*n*-octylphthalate are sufficiently well defined to allow assessments of the environmental fate of the compound to be made. Therefore, no additional information is needed a this time.

Production, Import/Export, Use, Release, and Disposal. Because of the general confusion in the literature about the nomenclature for octylphthalate esters, historical information about the production and import/export of di-*n*-octylphthalate is not readily available. These values generally must be estimated as a percentage of di(2-ethylhexyl)phthalate production or import/export. The compound is used principally as a plasticizer additive to plastics and PVC resins. It is also used as a dye carrier in plastics production and as a chemical intermediate (EPA 1993a; HSDB 1995; Mannsville Chemical Products Corporation 1989; Sittig 1991). Limited information is available about releases of di-*n*-octylphthalate to environmental media. Even the TRI data, which comprise the most current information available, contain errors as a result of the nomenclature confusion (EPA 1993a; Vista Chemical 1992). Data are available about the disposal and regulatory status of the compound (see Chapters 4 and 7). More information on the production and releases of di-*n*-octylphthalate is needed to estimate potential exposure to the compound.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1993, became available in May of 1995. This database will be updated yearly and should provide a list of industrial production

facilities and emissions. However, di-*n*-octylphthalate was withdrawn from the TRI effective in 1993 (EPA 1995h).

Environmental Fate. Di-*n*-octylphthalate partitions primarily to soils and sediment upon release to the environment. The compound is expected to be strongly sorbed to soil and sediment particulates; therefore, it should have limited mobility (EPA 1979, 1992c). Biodegradation half-lives of l-4 weeks have been estimated for aerobic surface waters and soils. Biodegradation also takes place in sediments; half-lives under anaerobic conditions have been estimated to range from of 6 months to 1 year (Howard et al. 1991). The compound may also undergo photolysis in surface waters (estimated half-life of 144 days) and photooxidation in the atmosphere (estimated half-life of about 5-45 hours) (Howard et al. 1991). Di-*n*-octylphthalate may persist in sediments as a result of its limited rate of biotransformation and preferential partitioning to this medium.

However, although degradation is known to occur under both aerobic and anaerobic conditions, data are not available on the identity of degradation products. Because the limited studies on the mechanisms of injury from di-*n*-octylphthalate suggest that mono-*n*-octylphthalate is the proximate toxicant, it is important to know whether the reduction of di-*n*-octylphthalate is coupled with the accumulation of mono-*n*-octylphthalate. The environmental fate of di-*n*-octylphthalate and its metabolites is not sufficiently understood to allow assessments of its exposure potential to be made. Additional data are needed on the identify and fate of degradation products of di-*n*-octylphthalate. No additional information is needed about the transport and partitioning of the compound at this time.

Bioavailability from Environmental Media. No information was found regarding the absorption of di-*n*-octylphthalate by humans or laboratory animals following inhalation or dermal exposures. No information is available about absorption following oral exposure in humans. However, indirect evidence from animal studies suggests that the compound is readily absorbed by this route (Albro and Moore 1974; Oishi 1990). Additional information is needed on the absorption of di-*n*-octylphthalate as a result of inhalation of contaminated air, ingestion of contaminated food and water, and dermal contact with contaminated soils and sediments.

Food Chain Bioaccumulation. Di-*n*-octylphthalate bioconcentrates in aquatic organisms. However, as a result of metabolism of the compound, biomagnification in aquatic food chains does not occur (EPA 1992d). It appears that the compound is not bioconcentrated by terrestrial plants or animals or biomagnified in terrestrial food chains (EPA 1986e; Wild and Jones 1992). However, the Wild and Jones (1992) study is limited to mathematical modeling results. Thus, only limited data are available regarding the bioaccumulation and biomagnification of di-*n*-octylphthalate, and the potential for human exposure resulting from the bioaccumulation of the compound is not well understood. Therefore, additional data are needed to validate the Wild and Jones (1992) model. Also, an estimation of animal uptake from soil ingestion is needed to support this study.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of di-n-octylphthalate in contaminated media at hazardous waste sites are needed so that the information obtained on levels of di-*n*-octylphthalate in the environment can be used in combination with the known body burden of di-*n*-octylphthalate to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Di-*n*-octylphthalate has been detected in ambient air, rain, surface water, groundwater, and sediment. However, as a result of the confusion about the nomenclature for octylphthalate esters, much of the historical monitoring data available actually pertain to the branched isomer, di(2-ethylhexyl)phthalate (Vista Chemical 1992). Therefore, little current information specific to the n-octyl isomer is available regarding concentrations of the compound in foods, drinking water, and environmental media, particularly with respect to media at hazardous waste sites. The lack of monitoring data precludes the estimation of human exposure via intake of or contact with contaminated media.

Exposure Levels in Humans. This information is necessary for assessing the need to conduct health studies on these populations. Di-*n*-octylphthalate has historically been reported to have been found in human adipose tissue (EPA 1986d). However, more recent information indicates that the compound detected was actually the branched di(Zethylhexy1) isomer (EPA 1989b). Additional information on the concentrations of di-*n*-octylphthalate in human tissues and fluids, parficularly for populations living near hazardous waste sites, is needed to assess potential human exposure to the compound.

Exposure Registries. No exposure registries for di-*n*-octylphthalate 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 exposure to this substance.

5.7.2 On-going Studies

No information was found in the available literature concerning on-going studies dealing with the environmental fate or human exposure potential of di-*n*-octylphthalate.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring di-*n*-octylphthalate, its metabolites, and other biomarkers of exposure and effect to di-*n*-octylphthalate. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally; analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Very limited data were found regarding the measurement of di-*n*-octylphthalate and its metabolites in biological fluids. Table 6-l summarizes the methods that are available. Analytical methods were located for measuring di-*n*-octylphthalate and its metabolites in urine, blood, and tissues (Albro and Moore 1974; Lanina et al. 1992; Oishi 1990). These methods include gas chromatography (GC) combined with mass spectrometry (MS) and high-performance liquid chromatography (HPLC) combined with an ultraviolet detector (UV). No comparisons can be made between methods since no data were given regarding sensitivity, recovery, or precision.

6.2 ENVIRONMENTAL SAMPLES

Table 6-2 summarizes the various methods available for measuring di-*n*-octylphthalate in environmental samples. GC/MS and GC combined with electron capture detection (ECD') can be used to measure di-*n*-octylphthalate in water, waste water, groundwater, soil, and solid waste (APHA 1992; Eichelberger et al. 1983; EPA 1981, 1986a, 1986b, 1986c, 1990b; Furtmann 1994; Lopez-Avila et al. 1989; Ritsema et al. 1989; Valkenburg et al. 1989).

TABLE 6-1. Analytical Methods for Determining Di-*n*-octylphthalate in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Extract compound from urine using diethyl ether; wash with HCl, dry over anhydrous Na_2SO_4, filter; evaporate diethyl ether; dissolve evaporated residue with diethyl ether	HPLC/UV; GC/MS	NR	NR	Albro and Moore 1974; Albro et al. 1973
Blood	Extract compound from blood using heptane[a]	GC	NR	NR	Lanina et al. 1992
Blood and tissue samples	Mix blood sample with HCl and hexane; homogenize tissue sample and mix with HCl and hexane; evaporate hexane; dissolve evaporated residue with methanol[a,b]	HPLC	NR	NR	Oishi 1990

[a]This method was reported for determining "dioctylphthalate"; thus, the precise identity of the substance being determined may not necessarily be di-*n*-octylphthalate.

[b]This method was reported for determining only mono-*n*-octylphthalate not di-*n*-octylphthalate.

GC = gas chromatography; HCl = hydrochloric acid; HPLC = high-performance liquid chromatography; MS = mass spectrometry; Na_2SO_4 = sodium sulfate; NR = not reported; UV = ultraviolet detector

TABLE 6-2. Analytical Methods for Determining Di-*n*-octylphthalate in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Extract serial with methylene chloride at pH >11 (pH 7 for capillary column) and pH 2; analyze extracts separately for packed column, combined for capillary column; dry over anhydrous sodium sulfate; concentrate; inject	GC/MS	1–10 µg/L	70–81	Eichelberger et al. 1983
Water	Extract serial with methylene chloride at pH >11 and pH <2; concentrate	GC/MS	NR	83.5–105.4	Valkenburg et al. 1989
Tap water	Extract compound with solid-phase extraction technique that uses a membrane impregnated with reverse-phase particles; elute with acetonitrile	LC	Low ppb (µg/L)	82–93	Hagen et al. 1990
Water, groundwater, waste water, landfill leachate	Solid-phase extraction activating with methanol; dry; elute with ethyl acetate/DAIP	GC/MS	0.02 µg/L	94	Furtmann 1994

TABLE 6-2. Analytical Methods for Determining Di-*n*-octylphthalate in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water, waste water	Extract with methylene chloride at pH >11 and again at pH <2; dry; concentrate	GC/MS	2.5 µg/L	4–146	APHA 1992
Waste water	Extract sample with dichloromethane/hexane at pH 2, 7, and 10; elute from Florisil or alumina with ether/hexane	GC/ECD	0.1 ng/injection	>90	EPA 1981
Waste water	Add stable isotopically labeled analogs of the compounds to 1 L of waste-water sample; extract sample at pH 12–13, then at pH <2, with methylene chloride using continuous extraction techniques; dry extract over sodium sulfate; concentrate; add internal standard; inject	GC/MS	10 µg/L	NR	EPA 1990b (Method 1625)

TABLE 6-2. Analytical Methods for Determining Di-*n*-octylphthalate in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Groundwater, soil, solid waste	Extract sample with methylene chloride; concentrate solvent; exchange to hexane	GC/ECD	30 µg/L (groundwater); 2 mg/kg (soil); 300 mg/kg (solid waste)	D[a]–114	EPA 1986c (Method 8060)
Groundwater, soil, solid waste	Extract with methylene chloride	GC/MS	25 µg/L (groundwater); 2 mg/kg (soil); 250 mg/kg (solid waste)	4–146	EPA 1986b (Method 8250)
Groundwater, soil	Extract with methylene chloride; gel permeation cleanup	GC/MS	660 µg/kg (soil); 10 µg/L (groundwater)	4–146	EPA 1986a (Method 8270)
Water/SPM	Collect water samples on disposable octyl-bonded silica solid-phase extraction columns; dry; elute with hexane/ether; SPM collected by continuous flow centrifugation; extract with acetone/water/benzene	GC/ECD; GC/MS	0.1 µg/L (water); 0.1 mg/kg (suspended particulate)	83 (water); 82 (suspended particulate)	Ritsema et al. 1989

TABLE 6-2. Analytical Methods for Determining Di-*n*-octylphthalate in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil, sediment, citrus leaves, coal, coal fly ash	Clean up sample using disposable Florisil cartridge; elute with methylene chloride in hexane and hexane/acetone	GC/ECD	NR	80–104	Lopez-Avila et al. 1989

[a]Detected, result greater than zero

DAIP = diallylphthalate; ECD = electron capture detection; GC = gas chromatography; LC = liquid chromatography; MS = mass spectrometry; NR = not reported; SPM = suspended particulate matter

Generally, sample preparation procedures involved extraction with methylene chloride at pH <2 and pH >11. The removal of interferents such as organochlorine pesticides and polychlorinated biphenyls has been approached though the addition of a clean-up step using Florisil columns (EPA 1981) and more recently solid-phase extraction alone with Florisil or other solid-phase matrices have been used (Furtmann 1994; Lopez-Avila et al. 1989; Ritsema et al. 1989). Sensitivity is in the low-ppb (µg/L) range for water samples using GC/MS (APHA 1992; Eichelberger et al. 1983; EPA 1986a, 1986b, 1990b; Furtmann 1994; Valkenburg et al. 1989). GC/MS provided slightly better sensitivity than did GC/ECD. For water samples, recoveries are good for GC/MS and GC/ECD (Eichelberger et al. 1983; EPA 1981; Furtmann 1994; Ritsema et al. 1989; Valkenburg et al. 1989). Precision was adequate (<13-21% relative standard deviation [RSD]) (Eichelberger et al. 1983; Valkenburg et al. 1989). For soil and solid waste samples, sensitivity was in the ppm (µg/L) range using GC/MS and GC/ECD. For the standard analytical methods approved by EPA (Test Methods 1625, 8060, 8250, and 8270) and APHA, recovery and precision varied greatly for both water and soil samples (APHA 1992; EPA 1986a, 1986b, 1986c, 1990b).

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 di-*n*-octylphthalate is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of di-*n*-octylphthalate.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect

Exposure. Methods for Determining Parent Compounds and Degradation Products in Environmental Media.Methods are available for measuring di-*n*-octylphthalate and/or its metabolites (primarily the corresponding phthalate monoesters) in urine, blood, and tissues (Albro and Moore 1974; Lanina et al. 1992; Oishi 1990); however, the data are very limited. More information on the accuracy, precision, and sensitivity of these methods is needed to evaluate the value of using the levels of di-*n*-octylphthalate and its metabolites (particularly in urine) as indicators of exposure. The lack of data for these methods makes it difficult to assess whether these methods are sufficiently sensitive to measure levels at which health effects might occur, as well as background levels in the population.

Effect. *No* biomarkers of effects caused by di-*n*-octylphthalate have been identified in humans or animals,

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods exist for measuring di-*n*-octylphthalate in water, groundwater, waste water, soil, and solid waste (APHA 1992; Eichelberger et al. 1983; EPA 1981, 1986a, 1986b, 1986c, 1990b; Furtmann 1994; Lopez-Avila et al. 1989; Ritsema et al. 1989; Valkenburg et al. 1989); however, the database is limited. More information on the accuracy and precision of these methods is needed to accurately compare them. No data were located for measuring di-*n*-octylphthalate in air. The lack of data on background levels in the environment, as well as levels at which health effects might occur, prevents an evaluation of whether the methods are sensitive enough. Research investigating the relationship between environmental levels and observed health effects could increase confidence in existing methods and indicate where improvements are needed. Analytical methods are needed for determining degradation products in all environmental media.

6.3.2 On-going Studies

No on-going analytical methods studies were located.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding di-*n*-octylphthalate in air, water, and other media are summarized in Table 7-l.

ATSDR has derived an MRL of 3 mg/kg/day for acute-duration oral exposure in humans; this MRL is based on a LOAEL of 1,000 mg/kg/day in rats (Lake et al. 1986).

ATSDR has derived an MRL of 0.4 mg/kg/day for intermediate-duration oral exposure in humans; this MRL is based on a NOAEL of 40.8 mg/kg/day in rats (Poon et al. 1995).

An oral reference dose (RfD) is currently pending by EPA (IRIS 1995).

Neither EPA or IARC has classified di-*n*-octylphthalate as to its carcinogenicity.

TABLE 7-1. Regulations and Guidelines Applicable to Di-*n*-octylphthalate

Agency	Description	Information	Reference
NATIONAL			
Regulations:			
a. Water:			
EPA OWRS	General permits under NPDES	Yes	EPA 1995c (40 CFR 122, Appendix D)
	General Pretreatment Regulations for Existing and New Sources of Pollution	Yes	EPA 1995d (40 CFR 403, Appendix B)
b. Food:			
FDA	Component of adhesives	Yes	FDA 1995a (21 CFR 175.105)
	Use in rubber articles intended for repeated use	Yes	FDA 1995b (21 CFR 177.2600)
c. Other:			
EPA OERR	Reportable quantity	5000 pounds	EPA 1995i (40 CFR 302.4)
EPA OSW	Hazardous Waste Constituent (Appendix VIII)	Yes	EPA 1995f (40 CFR 261, Appendix VIII)
	Groundwater Monitoring List (Appendix IX)	Yes	EPA 1995g (40 CFR 264, Appendix IX)
	Land Disposal Restrictions	Yes	EPA 1995e (40 CFR 268)
EPA OTS	Toxic Chemical Release Reporting Rule	No[a]	EPA 1995h (40 CFR 372)
	Health and Safety Data Reporting Rule	No	EPA 1995b (40 CFR 716.120)
	Preliminary Assessment Information Reporting Rule	Yes	EPA 1995a (40 CFR 712.30)

[a]Delisted, effective 10/05/93. "EPA concluded that there is not sufficient evidence to establish that DNOP causes adverse acute human health effects, chronic human health effects, or environmental toxicity." [FR 58(19):51785].

EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NPDES = National Pollutant Discharge Elimination System; OERR = Office of Emergency and Remedial Response; OSW = Office of Solid Waste; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards

8. REFERENCES

Al-Badry MS, Knowles CO. 1980. Phthalate-organophosphate interactions: Toxicity, penetration, and metabolism studies with house flies. Arch Environ Contam Toxicol 9:147-161.

Alaimo LH, Hartman TG, Rosen RT, et al. 1990. Nonpriority analysis of the wastewater streams of four dye manufacturing facilities. Res J WPCF 62:665-669.

*Albro PW, Moore B. 1974. Identification of the metabolites of simple phthalate diesters in rat urine. J Chromatogr 94:209-218.

*Albro PW, Thomas R, Fishbein L. 1973. Metabolism of diethylhexyl phthalate by rats: Isolation and characterization of the urinary metabolites. J Chromotogr 76:321-330.

*APHA. 1992. American Public Health Association. Standard methods for the examination of water and wastewater. 18th Edition. Washington, DC: American Public Health Association.

Armstrong VC, Newhook RC. 1992. Assessing the health risks of priority substances under the Canadian environmental protection act. Regulatory Toxicol Pharmacol 15:111-121.

*ATSDR. 1988. Health assessment for Dixie Caverns Landfill, Salem, Virginia. Agency for Toxic Substances and Disease Registry, Atlanta, GA. PB90-144478.

ATSDR. 1989a. Decision guide for identifying substance-specific data needs related to toxicological profiles. Agency for Toxic Substances and Disease Registry. Federal Register 54:37618-37634.

*ATSDR. 1989b. Health assessment for Butler Mine Tunnel, Pittson, Pennsylvania. Agency for Toxic Substances and Disease Registry, Atlanta, GA. PB90-143603.

*ATSDR. 1989c. Health assessment for Revere Chemical Company National Priorities List (NPL) site, Revere Bucks County, Pennsylvania. Agency for Toxic Substances and Disease Registry, Atlanta, GA. PB90-144759.

*ATSDR. 1992. Toxicological profile for di(2-ethylhexyl)phthalate. Agency for Toxic Substances and Disease Registry, Atlanta, GA.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486. -.

Bennett GF. 1989. Impact of toxic chemicals on local wastewater treatment plant and the environment. Environ Geol Water Sci 3:201-212.

*Cited in text

8. REFERENCES

Bernstein ME. 1984. Agents affecting the male reproductive system: Effects of structure on activity. Drug Metab Rev 15:941-996.

Bower RK, Haberman S, Minton PD. 1970. Teratogenic effects in the chick embryo caused by esters of phthalic acid. J Pharmacol Exp Ther 171:314-324.

*Brodsky J, Andersson JT, Ballschmiter K. 1986. Chemical degradation of xenobiotics: II. Simulation of the biotic transformation of bis(Zethylhexy1) phthalate and dioctylphthalate by abiotic means. Chemosphere 15:139-147.

Brunetti G, Moscato G. 1984. Bronchial asthma due to occupational exposure to DOP. Med Lav 75:120-124.

Carmignani GM, Bennett JP. 1976. Leaching of plastics used in closed aquaculture systems. Aquaculture 7 :89-9 1.

*Carter JH, Richmond RE, Carter HW, et al. 1992. Quantitative image cytometry of hepatocytes expressing gamma-glutamyl transpeptidase and glutathione S-transferase in diethylnitrosamine-initiated rats treated with phenobarbital and/or phthalate esters. J Histochem Cytochem 40: 1105-l 115.

*Clayton GD, Clayton FE, eds. 1981. Patty's industrial hygiene and toxciology. Volume 2A: Toxicology. 3rd revised ed. New York, NY: John Wiley and Sons, 2343-2351.

*Cole RH, Frederick RE, Healy RP, et al. 1984. Preliminary findings of the priority pollutant monitoring project of the Nationwide Urban Runoff Program. Journal WPCF 56(7):898-908.

Comu MC, Lhuguenot JC, Brady AM, et al. 1992. Identification of the proximate peroxisome proliferators derived from di(ethylhexy1) adipate and species differences in response. Biochem Pharmacol 43:2129-2134.

*DeAngelo AB, Garrett CT, Manolukas LA, et al. 1986. Di-*n*-octyl phthalate (DOP), a relatively ineffective peroxisome inducing straight chain isomer of the environmental contaminant di(2-ethylhexyl)phthalate (DEHP), enhances the development of putative preneoplastic lesions in rat liver. Toxicology 41:279-288.

*DeLeon IR, Byrne CJ, Peuler EA, et al. 1986. Trace organic and heavy metal pollutants in the Mississippi River. Chemosphere 15(6):795-805.

Dillingham EO, Autian J. 1973. Teratogenicity, mutagenicity, and cellular toxicity of phthalate esters. Environ Health Perspect 81-89.

Dirven HA, Theuws JL, Jongeneelen FJ, et al. 1991. Non-mutagenicity of 4 metabolites of di(2-ethylhexyl)phthalate (DEHP) and 3 structurally related derivatives of di(2-ethylhexyl)adipate (DEHA) in the salmonella mutagenicity assay. Mutat Res 260:121-130.

*Dogra RK, Chandra K, Chandra S, et al. 1989. Di-octyl phthalate induced altered host resistance: Viral and protozal models in mice. Industrial Health 27:83-87.

8. REFERENCES

*Dogra RK, Khanna S, Nagale SL, et al. 1985. Effect of dioctyl phthalate on immune system of rat. Indian J Exp Bio 23:315-319.

*Dogra RK, Khanna S, Shukla L, et al. 1987. Modification of the immune response in rats by di-octyl phthalate. Industrial Health 25:97-101.

*Eastman Kodak Company. 1978. Toxicity and health hazard summary. Rochester, NY: EPA/OTS Document No. 878214345.

*Eichelberger JW, Kerns EH, Okynyk P, et al. 1983. Precision and accuracy in the determination of organics in water by fused silica capillary column gas chromatography/mass spectrometry and packed column gas chromatography/mass spectrometry. Anal Chem 55:1471-1479.

*EPA. 1979. Water-related environmental fate of 129 priority pollutants. Volume II. Washington, DC: Monitoring and Data Support Division, U.S. Environmental Protection Agency. EPA Report No. 440/4-79-029b, 94: l-28.

EPA. 1980. U.S. Environmental Protection Agency. Federal Register 45:33132-33133.

*EPA. 1981. Determination of phthalates in industrial and municipal waste waters. Technical report. Cincinnati, OH: U.S. Environmental Protection Agency. EPA-600/4-81-063.

EPA. 1982. Aquatic fate process data for organic priority pollutants. Washington, DC: Monitoring and Data Support Division, Office of Water Regulations and Standards, U.S. Environmental Protection Agency. EPA Report No. 440/4-81-014.

EPA. 1985. U.S. Environmental Protection Agency. 40 CFR 122.1, 122 Appendix D.

*EPA. 1986a. Test methods for evaluating solid waste (SW-846). Volume IC: Laboratory manual physical/chemical methods. Method 8270. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1986b. Test methods for evaluating solid waste (SW-846). Volume IC: Laboratory manual physical/chemical methods. Method 8250. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1986c. Test methods for evaluating solid waste (SW-846). Volume IC: Laboratory manual physical/chemical methods. Method 8060. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1986d. Broad scan analysis of the FY82 national human adipose tissue survey specimens. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances.

*EPA. 1986e. Toxic and priority organics in municipal sludge land treatment systems. Cincinnati, OH: Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development, Wastewater Engineering Research Laboratory. EPA/600/2-86/010.

*EPA. 1987a. Health and environmental effects profile for phthalic acid esters (PAEs). Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. PB89-120158.

8. REFERENCES

*EPA. 1987b. Health effects assessment for selected phthalic acid esters. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development. PB88-178934.

EPA. 1987c. U.S. Environmental Protection Agency. Part II. Federal Register 52:25942-25953.

EPA. 1987d. U.S. Environmental Protection Agency. Part II. Federal Register 52:13370, 13379-13381.

EPA. 1988a. U.S. Environmental Protection Agency. 40 CFR 401.16, 403, APPENDIX B

EPA. 1988b. U.S. Environmental Protection Agency. Part II. Federal Register 53:4500-4507.

EPA. 1988c. U.S. Environmental Protection Agency. Part V. Federal Register 53:38642-38654.

EPA. 1989a. U.S. Environmental Protection Agency final report. NHATS broad scan analysis: Population estimates from fiscal year 1982 specimens. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances. EPA 560/5-90-001.

*EPA. 1989b. U.S. Environmental Protection Agency. Part V. Federal Register 54:33418-33419, 33457.

*EPA. 1990a. Interim methods for development of inhalation reference doses. Washington, DC: U.S. Environmental Protection Agency. EPA/600/8-90/066A.

*EPA. 1990b. Method 1625 revision B. Semivolatile organic compounds by isotope dilution GCYMS. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR Ch.l:516-536.

EPA. 1990c. U.S. Environmental Protection Agency. Part II. Federal Register 55:22520-22537, 22593, 22712.

EPA. 1991a. U.S. Environmental Protection Agency. 40 CFR 261, Appendix VIII.

EPA. 1991b. U.S. Environmental Protection Agency. Part II. Federal Register 55:3864-3910.

*EPA. 1992a. Chemistry report on di-*n*-octylphthalate. Washington, DC: Industrial Chemistry Branch, Economics and Technology Division, Office of Toxic Substances, U.S. Environmental Protection Agency.

*EPA. 1992b. Heast Table 1: Subchronic and chronic toxicity (other than carcinogenicity). Health Effects Assessment Summary Tables. U.S. Environmental Protection Agency. NTIS Order No. PB92-921199.

*EPA. 1992c. Di-*n*-octylphthalate exposure report for delisting petition. U.S. Environmental Protection Agency, Washington, DC. Memorandum from Annett Nold, Exposure Assessment Branch, Exposure Evaluation Division, Office of Pollution Prevention and Toxics to Ken Mitchell, Toxics Release Inventory Management Staff, Economics and Technology Division, Office of Pollution Prevention and Toxics. September 21, 1992.

8. REFERENCES

*EPA. 1992d. Transmittal of hazard assessment of di-*n*-octyl phthalate. Washington, DC: U.S. Environmental Protection Agency, Washington, DC. Memorandum from Lorraine Randecker, Chemical Review and Evaluation Branch, Health and Environmental Review Division, Office of Pollution Prevention and Toxics to Ken Mitchell, Toxics Release Inventory Management Staff, Economics and Technology Division, Office of Pollution Prevention and Toxics. July 15, 1992.

*EPA. 1993a. Di-*n*-octyl phthalate; toxic chemical release reporting; community right-to-know. U.S. Environmental Protection Agency. Federal Register 58(8):4133-4137.

*EPA. 1993b. Di-*n*-octyl phthalate; toxic chemical release reporting; community right-to-know. U.S. Environmental Protection Agency. Federal Register 58(191):51785-51786.

EPA. 1993c. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 372 Subpart D.

*EPA. 1995a. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 712.30.

*EPA. 1995b. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 716.120.

*EPA. 1995c. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 122 Appendix D.

*EPA. 1995d. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 403 Appendix B .

*EPA. 1995e. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 268.

*EPA. 1995f. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 261 Appendix VIII.

*EPA. 1995g. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 264 Appendix IX.

*EPA. 1995h. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 372.

*EPA. 19951. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 175.105.

FDA. 1977. Food and Drug Administration, Health and Human Services. 21 CFR 175.105.

FDA. 1992. Food and Drug Administration, Health and Human Services. 21 CFR 177.2600.

*FDA. 1995a. U.S. Food and Drug Administration. Code of Federal Regulations 21 CI% 175.105.

*FDA. 1995b. U.S. Food and Drug Administration. Code of Federal Regulations 21 CFR 177.2600.

Ferrario JB, DeLeon IR, Tracy RE. 1985. Evidence for toxic anthropogenic chemicals in human thrombogenic coronary plaques. Arch Environ Contam Toxicol 14:529-534.

8. REFERENCES

*Florin I, Rutberg L, Curvall M, et al. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology 18219-232.

*Foster PM, Thomas LV, Cook MW, et al. 1980. Study of the testicular effects and changes in zinc excretion produced by some n-alkyl phthalates in the rat. Toxicol Appl Pharmacol 54:392-398.

Fracasso A, Bazzato G, Kurtzman NA, et al. 1986. Plasticizers from peritoneal dialysis tubing and bags inhibit water transport *in vitro*. Clinical Res 34:729A.

*Fredricsson B, Moeller L, Pousette A, et al. 1993. Human sperm motility is affected by plasticizers and diesel particle extracts. Pharmacol Toxicol (Copenhagen) 72(2):128-133.

*Furtmann K. 1994. Phthalates in surface water-a method for routine trace level analysis. Fresenius' Journal of Analytical Chemistry 348(4):291-296.

Gangolli SD. 1982. Testicular effects of phthalate esters. Environ Health Perspect 45:77-84.

Garrett NE, Lewtas J. 1983. Cellular toxicity in Chinese hamster ovary cell cultures: I. Analysis of cytotoxicity endpoints for twenty-nine priority pollutants. Environ Res 32:455-465.

Geertz W, Dyer K, Johnson D, et al. 1974. Polyvinyl chloride biomedical products: Toxicity testing and identification of additives. Trans Am Sot Artif Int Organs 42-46.

Gesler RM. 1973. Toxicology of di-2-ethylhexyl phthalate and other phthalic acid ester plasticizers. Environ Health Perspect 73-79.

Giam CS, Wong MK. 1987. Plasticizers in food. J Food Protection 50:769-782.

Goldstein DB, Feistner GJ, Faull KF, et al. 1987. Plasticizers as contaminants in commercial ethanol. Alcoholism: Clinical and Experimental Research 11:521-524.

*Goodyear Tire and Rubber Company. 1981a. Mutagenicity evaluation of dopine (dioctyl phthalate), BASF, Tank 28. *Salmonella typhimurium*/microsome bioassay. Akron, OH: Goodyear Tire and Rubber Company Laboratory Report No. 80-l l-5.

*Goodyear Tire and Rubber Company. 1981b. DNA Damage by dioctyl phthalate BASF, Tank 28 in the *E. coli* Pol A,- Assay. Akron, OH: Goodyear Tire and Rubber Company Laboratory Report No. 81-42-2.

*Gray TJ, Butterworth KR. 1980. Testicular atrophy produced by phthalate esters. Arch Toxicol Suppl 4:452-455.

Guess WL, Haberman S. 1968. Toxicity profiles of vinyl and polyolefinic plastics and their additives. J Biomed Mater Res 2:313-335.

*Hardin BD, Schuler RL, Burg JR, et al. 1987. Evaluation of 60 chemicals in a preliminary developmental toxicity test. Teratogenesis Carcinogen Mutagen 7:29-48.

8. REFERENCES

*HazDat. 1995. Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.

*Heindel JJ, Gulati DK, Mounce RC, et al. 1989. Reproductive toxicity of three phthalic acid esters in a continuous breeding protocol. Fundam Appl Toxicol 12:508-518.

*Hinton RH, Mitchell FE, Mann A, et al. 1986. Effects of phthalic acid esters on the liver and thyroid. Environ Health Perspect 70:195-210.

*Howard PH, Boethling RS, Jarvis WF, et al., eds. 1991. Handbook of environmental degradation rates, New York, NY: Lewis Publishers.

*HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology-Information Program, Bethesda, MD.

Hüls AG. 1989. Phthalic acid, di-*n*-octylphthalate, n-decyl ester: Bacterial mutation assay. Huntingdon Research Centre. Huntingdon, England. DNN 64/901441.

*IRIS. 1995. Integrated Risk Information System. U.S. Environmental Protection Agency, Washington, DC. March 13, 1995.

Johnson BT, Heitkamp MA, Jones JR. 1984. Environmental and chemical factors influencing the biodegradation of phthalic acid esters in freshwater sediments. Environ Pollut 8:101-l 18.

Jones AE, Kahn RH, Groves JT, et al. 1975. Phthalate ester toxicity in human cell cultures. Toxicol Appl Pharmacol 31:283-289.

*Jones HB, Garside DA, Liu R, et al. 1993. The influence of phthalate esters on Leydig cell structure and function *in vitro* and *in vivo.* Exp Mol Path01 58(3):179-193.

Jones TD, Walsh PJ, Zeighami EA. 1985. Permissible concentrations of chemicals in air and water derived from RTECS entries: A “rash” chemical scoring system. Toxicol Ind Health 1:213-234.

*Jungclaus GA, Lopez-Avila V, Hites RA. 1978. Organic compounds in an industrial wastewater: A case study of their environmental impact. Environ Sci Technol 12:88-96.

Kalman DA. 1986. Survey analysis of volatile organics released from plastics under thermal stress, Am Ind Hyg Assoc J 47:270-275.

Kandala JC, DeAngelo AB, Reddy TV, et al. 1993. Transcriptional changes in hepatic tumors of rats induced by di(2-ethylhexyl) phthalate and di-*n*-octyl phthalate. Environmental Science (Tokyo) 2(3):147-159.

Kaya K, Nohara K. 1987. Effect of di-*n*-octyl phthalate on fatty acid composition of phosphatidylcholine in *tetrahymena.* Chem Biol Interactions 64:93-101.

Khanna S, Dogra RK, Bhatnagar MC, et al. 1989. Light and electronmicroscopic changes in testis of di-octyl phthalate treated rats. J Environ Biol 10:355-362.

8. REFERENCES

Klaunig JE, Ruth RJ, DeAngelo AB, et al. 1988. Inhibition of mouse hepatocyte intercellular communication by phthalate monoesters. Cancer Lett 43:65-71.

Kluwe WM. 1982. Overview of phthalate ester pharmacokinetics in mammalian species. Environ Health Perspect 45:3-9.

Kluwe WM, McConnell EE, Huff JE, et al. 1982. Carcinogenicity testing of phthalate esters and related compounds by the National Toxicology Program and the National Cancer Institute. Environ Health Perspect 45:129-133.

Kondyli E, Demertzis PG, Kontominas MG. 1992. Migration of dioctylphthalate and dioctyladipate plasticizers from food-grade PVC films into ground-meat products. Food Chem 45:163-168.

Kool HJ, van Kreijl CF, Zoeteman CJ. 1983. Toxicology assessment of organic compounds in drinking water. CRC Criteria1 Reviews in Environmental Control 12:307-357.

Korhonen A, Hemminki K, Vainio H. 1983a. Embryotoxic effects of phthalic acid derivatives, phosphates and aromatic oils used in the manufacturing of rubber on three day chicken embryos. Drug Chem Toxicol 6:191-207.

Korhonen A, Hemminki K, Vainio H. 1983b. Toxicity of rubber chemicals towards three-day chicken embryos. Stand J Work Environ Health 9:115-119.

*Lake BG, Gray TJ, Gangolli SD. 1986. Hepatic effects of phthalate esters and related compounds - *in vivo* and *in vitro* correlations. Environ Health Perspect 67:283-290.

*Lake BG, Phillips JC, Linnell JC, et al. 1977. The *in vitro* hydrolysis of some phthalate diesters by hepatic and intestinal preparations from various species. Toxicol Appl Pharmacol 39:239-248.

*Lake BG, Rijcken WR, Gray TJ, et al. 1984. Comparative studies of the hepatic effects of di- and mono-*n*-octyl phthalates, di-(Zethylhexyl) phthalate and clofibrate in the rat. Acta Pharmacol Toxicol 54:167-176.

*Lanina SY, Strakhova NM, Lappo VG. 1992. Toxicological estimate of polyvinyl chloride containers for preparation and storage of blood, its components, preservatives and infusion solutions. Med Prog Tech 18:19-22.

*Ligocki MP, Leuenber C, Pankow JF. 1985. Trace organic compounds in rain: II. Gas scavenging of neutral organic compounds. Atmospheric Environ 19(10):1609-1617.

*Lopez-Avila V, Milanes J, Dodhiwala NS, et al. 1989. Cleanup of environmental sample extracts using florisil solid-phase extraction cartridges. J Chromatogr Sci 27(5):209-220.

Mabey WR, Smith JH, Pod011 RT, et al. 1982. Aquatic fate process data for organic priority pollutants. Report to U.S. Environmental Protection Agency, Office of Water Regulations and Standards, Washington, DC, by SRI International, Menlo Park, CA. EPA 440/4-81-014.

Mallette FS, von Haam E. 1952. Studies on the toxicity and skin effects of compounds used in the rubber and plastics industries. Ind Hyg Occup Med 231-236.

8. REFERENCES

*Mann AH, Price SC, Mitchell FE, et al. 1985. Comparison of the short-term effects of di(2-ethylhexyl) phthalate, di(n-hexyl)phthalate, and di(n-octyl)phthalate in rats. Toxicol Appl Pharmacol 77:116-132.

*Mannsville Chemical Products Corporation. 1989. Dioctyl phthalate. Chemical products synopsis, Mannsville Chemical Products Corporation, Asbury Park, NJ.

*Mathur SP. 1974a. Phthalate esters in the environment: Pollutants or natural products? J Environ Qua1 3(3):189-197.

*Mathur SP. 1974b. Respirometric evidence of the utilization of di-octyl and di-2-ethylhexyl phthalate plasticizers. J Environ Quality 3:207-209.

*Morrissey RE, Lamb JC, Morris RW, et al. 1989. Results and evaluations of 48 continuous breeding reproduction studies conducted in mice. Fundam Appl Toxicol 13:747-777.

*NAS/NRC. 1989. Biologic markers in reproductive toxicology. National Academy of Sciences/National Research Council. Washington, DC: National Academy Press, 15-35.

Nematollahi J, Guess WL, Autian J. 1967. Plasticizers in medical application: I. Analysis and toxicity evaluation of dialkyl benzenedicarboxylates. J Pharmacol Sci 56:1446-1453.

*NIOSH. 1983. Screening of priority chemicals for potential reproductive hazard. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control. NTIS Order No. PB85-220143.

*NIOSH. 1993. National Occupational Exposure Survey. Cincinnati, OH: National Institute for Occupational Safety and Health, Centers for Disease Control. March 10, 1993.

*NIOSH RTECS. 1987. Registry of toxic effects of chemical substances. 1985-1986 Edition. Volume 4. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, 3461.

NTP. 1982a. NTP technical bulletin. Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services, 7.

NTP. 1982b. NTP technical bulletin. Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services, 8.

*NTP. 1985. Di-*n*-octylphthalate: Reproduction and fertility assessment in CD-l mice when administered in feed. Research Triangle Park, NC: National Institute of Environmental Health Sciences, National Toxicology Program. NTP-85-140. NTIS Order No. PB85-218147.

*Oishi S. 1990. Effects of phthalic acid esters on testicular mitochondrial functions in the rat. Arch Toxicol 64:143-147.

*Oishi S, Hiraga K. 1980. Testicular atrophy induced by phthalic acid esters: Effect on testosterone and zinc concentrations. Toxicol Appl Pharmacol 53:35-41.

8. REFERENCES

*Oishi S, Hiraga K. 1982. Effects of monoesters of O-phthalic acid on serum lipid composition of rats. Toxicol Lett 14:79-84.

Perwak, Goyer M, Schimke G, et al. 1980. An exposure and risk assessment for phthalate esters. Final draft report. Washington, DC: U.S. Environmental Protection Agency, Office of Water and Waste Management.

*Peterson JC, Freeman DH. 1984. Variations of phthalate ester concentrations in sediments from the Chester River, Maryland. Inter J Environ Anal Chem 18:237-252.

*Petrasek AC, Kugelman IJ, Austern BM, et al. 1983. Fate of toxic organic compounds in wastewater treatment plants. J WPCF 55:1286-1296.

Phillips LJ. 1992. Regional relationships between toxic releases, and environmental and human exposure to toxic substances. Bull Environ Contam Toxicol 48:795-802.

*Peon R, Lecavalier P, Mueller R, et al. 1995. Subchronic oral toxicity of di-*n*-octylphthalate and di(2-ethylhexyl)phthalate in the rat. [ATSDR peer-reviewed draft].

*Ritsema R, Cofino WP, Frintop PCM, et al. 1989. Trace-level analysis of phthalate esters in surface water and suspended particulate matter by means of capillary gas chromatography with electron-capture and mass-selective detection. Chemosphere 18:2161-2175.

Russell D, McDuffie B. 1986. Chemodynamic properties of phthalate esters: Partitioning and soil migration. Chemosphere 15:1003-1021.

Sabatini S, Fracasso A, Bazzato G, et al. 1989. Effect of phthalate acid esters on transport in toad bladder membrane. J Pharmacol Exp Ther 250:910-914.

Sanborn JR, Metcalf RL, Yu CC, et al. 1975. Plasticizers in the environment: The fate of di-*n*-octyl phthalate (DOP) in two model ecosystems and uptake and metabolism of DOP by aquatic organisms. Arch Environ Contam Toxicol 3:244-255.

*Sato T, Nagase H, Sato K, et al. 1994. Enhancement of the mutagenicity of amino acid pyrolysates by phthalate esters. Environ Mol Mut 24:325-331.

*Sax NI, Lewis RJ Sr. 1989. Dangerous properties of industrial materials. Volume II, 7th ed. New York, NY: Van Nostrand Reinhold, 1465-1466.

Schwartz BS, Ford DP, Bolla KI, et al. 1990. Solvent-associated decrements in olfactory function in paint manufacturing workers. Am J Ind Med 18:697-706.

*Seed JL. 1982. Mutagenic activity of phthalate esters in bacterial liquid suspension assays. Environ Health Perspect 45:111-114.

Shafer KH, Cooke M, DeRoos F, et al. 1981. WCOT capillary column GC/FT-IR and GC/MS for identifying toxic organic pollutants. Appl Spectroscopy 35:469-472.

8. REFERENCES

*Shelton DR, Boyd SA, Tiedje JM. 1984. Anaerobic biodegradation of phthalic acid esters in sludge. Environ Sci Technol 18:93-97.

*Shibamoto T, Wei CI. 1986. Mutagenicity of materials extracted from synthetic rubber. Agric Biol Chem 50:513-514.

*Singh AR, Lawrence WH, Autian J. 1972. Teratogenicity of phthalate esters in rats. J Pharm Sci 61(1):51-55.

*Sittig M. 1991. Handbook of toxic and hazardous chemicals and carcinogens. Volume 1, 3rd ed. Park Road, NJ: Noyes Publications, 674-675.

*Stutz DR, Ulin S. 1992. Hazardous materials injuries: A handbook for pre-hospital care. Third edition. Beltsville, MD: Bradford Communications Corporation, 258-259.

Sugawara N. 1974. Toxic effect of a normal series of phthalate esters on the hatching of shrimp eggs. Toxicol Appl Pharmacol 30:87-89.

*Tabak HH, Quave SP, Mashni CI, et al. 1981. Biodegradability studies with organic priority pollutant compounds. J Water Quality 1503-1517.

Takagi A, Sai K, Umemura T, et al. 1990. Significant increase of 8-hydroxyguanosine in liver DNA of rats following short-term exposure to the peroxisome proliferators di(2-ethylhexyl)phthalate and di(2-ethylhexyl)adipate. Jpn J Cancer Res 81:213-215.

Takahashi T. 1977. Biochemical studies on phthalic esters: II. Effects of phthalic esters on mitochondrial respiration of rat liver. Biochem Pharmacol 26: 19-24.

Teranishi H, Kasuya M. 1980. The effects of phthalate esters on fibroblasts in primary culture. Toxicol Lett 6:11-15.

*TRI92. 1994. Toxic Chemical Release Inventory. U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC.

Urushigawa Y, Yonezawa Y. 1979. Chemico-biological interactions in biological purification systems: VI. Relation between biodegradation rate constants of di-*n*-alkyl phthalate esters and their retention times in reverse phase partition chromatography. Chemosphere 5:317-320.

USITC. 1986. Synthetic organic chemicals: United States production and sales. Washington, DC: United States International Trade Commission.

USITC. 1989. Synthetic organic chemicals: United States production and sales. Washington, DC: United States International Trade Commission.

*USITC. 1994. Synthetic organic chemicals: United States production and sales. Washington, DC: United States International Trade Commission.

8. REFERENCES

*Valkenburg CA, Munslow WD, Butler LC. 1989. Evaluation of modifications to extraction procedures used in analysis of environmental samples from Superfund sites. J Assoc Off Anal Chem 72(4):602-608.

*Vista Chemical Company. 1992. Petition to delist di-*n*-octylphthalate under Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986. Submitted to U.S. Environmental Protection Agency. Austin, TX.

Walker JD. 1990. Review of chemical fate testing conducted under section 4 of the toxic substances control act: Chemicals, tests, and methods. J Bacterial 13:78-90.

*Wang YY, Marsden PJ, Flessel CP, et al. 1990. Evaluation and validation of protocols for measurement of the mutagenicity of environmental samples. In: Friedman D, ed. Waste testing and quality assurance: Second volume. STP 1062.

*Wild SR, Jones KC. 1992. Organic chemicals entering agricultural soils in sewage sludges: Screening for their potential to transfer to crop plants and livestock. Sci Total Environ 119:85-l 19.

Williams DF. 1981. The toxicology of additives in medical plastics. In: Williams DF, ed. Systemic aspects of biocompatibility. Volume II. Boca Raton, FL: CRC Press, Inc., 145-157.

*Wolfe NL, Burns LA, Steen WC. 1980. Use of linear free energy relationships and an evaluate model to assess the fate and transport of phthalate esters in the aquatic environment. Chemosphere 9:393-402.

Yu X, Wang X, Bartha R, et al. 1990. Supercritical fluid extraction of coal tar contaminated soil. Environ Sci Technol 24:1732-1738.

*Zeiger E, Haworth S, Mortelmans K, et al. 1985. Mutagenecity testing of di(Zethylhexyl)phthalate and related chemicals in salmonella. Environ Mutagen 7:213-232.

*Zeiger E, Haworth S, Speck W, et al. 1982. Phthalate ester testing in the National Toxicology Program's environmental mutagenesis test development program. Environ Health Perspect 45:99-101.

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.

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.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

9. GLOSSARY

q_1 * -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually 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. 3 11 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a 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

MINIMAL RISK LEVEL WORKSHEETS

Chemical Name: Di-*n*-octylphthalate
CAS Number: 117-84-0
Date: December 1995
Profile Status: Post-Public Comment - Draft 3
Route: [ ] Inhalation [x] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 5
Species : Rat

Minimal Risk Level: 3 [x] mg/kg/day [ ] ppm

Reference: Lake et al. 1986

Experimental design: Di-*n*-octylphthalate was administered (1,000 mg/kg/day) once/day for 14 days to a group of 4-6 male Sprague-Dawley rats. A group of male rats, administered the corn oil vehicle, served as controls. Following the last dose, animals were starved overnight and killed by cervical dislocation. Livers were excised to be weighed, then used for biochemical assays; histopathological examination was not performed.

Effects noted in study and corresponding doses: Liver effects were observed in treated rats. The hepatic effects consisted of a statistically significant ($p < 0.01$) increase (17 %) in relative liver weight and a reduction (approximately 30%) in 7-ethoxycoumarin *O*-deethylase activity relative to the vehicle control. Enzymatic indicators of peroxisome proliferation (KCN-insensitive palmitoyl-CoA oxidation or enoyl-CoA hydratase heat labile activity) were not significantly altered compared to controls. No significant changes in P-450 content or in the following activities were noted: ethylmorphine-*N*-demethylase, lauric acid 1 1-hydroxylation, and lauric acid 12-hydroxylation.

Dose and end point used for MRL derivation:

[ ] NOAEL [x] LOAEL (DOSE: 1000 mg/kg/day)

Uncertaintv Factors used in MRL derivation:

[x] 3 for use of a minimal LOAEL
[x] 10 for extrapolation from animals to humans
[x] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose? No. If so, explain:

If an inhalation study in animals. list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information which lend support to this MRL: The choice of liver toxicity as the basis for the acute oral MRL is supported by similar effects seen in other acute- and intermediate-duration studies in rats (DeAngelo et al. 1986; Lake et al. 1984; Mann et al. 1985).

APPENDIX A

Chemical Name: Di-*n*-octylphthalate
CAS Number: 117-84-0
Date: December 1995
Profile Status: Post-Public Comment - Draft 3
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 2 1
Species: Rat

Minimal Risk Level: 0.4 [x] mg/kg/day [ ] ppm

Reference: Poon et al. 1995

Experimental design: Groups of 10 male and 10 female Sprague-Dawley rats were maintained on diets containing 0, 5, 50, 500, or 5,000 ppm di-*n*-octylphthalate (DNOP) in the diet for 13 weeks. The study authors determined that these dietary concentrations corresponded to doses of 0, 0.4, 3.5, 36.8, 350.1 mg/kg/day (males) and 0, 0.4, 4.1, 40.8, 402.9 mg/kg/day (females). Control animals received feed containing 4% corn oil. The rats were examined daily for clinical signs of toxicity, while food consumption and body weight data were collected weekly. At the end of the study, the animals were anesthetized with an i.p. injection of pentobarbital. Blood was collected from the aortic artery for hematological and biochemical determinations; enzymatic activity assays and comprehensive histopathological examinations were performed (although only data on the liver, thyroid, testis, and epididymis were presented).

Effects noted in study and corresponding doses: No clinical signs of toxicity or reduction in food consumption or body weight gain were noted. No treatment-related changes in organ weights were noted. At 5,000 ppm, increased ($p < 0.05$) calcium was noted in males. Liver effects observed in rats administered di-*n*-octylphthalate in the diet at a concentration of 5,000 ppm; the study authors calculated the doses at this concentration to be 350.1 mg/kg/day (males) and 402.9 mg/kg/day (females) (Peon et al. 1995). The hepatic effects consisted of a significant ($p < 0.05$) increases in ethoxyresorufin-0-deethylase activity (12-fold, males; 3-fold, females); no significant changes were noted in liver aminopyrine-N-demethylase or aniline hydrolase activities. Also, at 5,000 ppm, histopathological changes in hepatic architecture were noted, including moderate accentuation of zonation and mild-to-moderate increases in perivenous cytoplasmic vacuolation. Mild histological changes in the thyroid were also noted at 5,000 ppm that consisted of reduction in the follicle size and decreased colloid density. No effects were observed at 500 ppm (36.8 mg/kg/day for males and 40.8 mg/kg/day for females). The MRL was derived by dividing the NOAEL value of 40.8 mg/kg/day for hepatic effects by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Dose and end point used for MRL derivation:

[x] NOAEL (DOSE: 40.8 mg/kg/day) [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 10 for extrapolation from animals to humans
[x] 10 for human variability

APPENDIX A

Was a conversion used from ppm in food or water to a mg/body weight dose? No.
If so, explain:

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information which lend support to this MRL: The choice of liver toxicity as the basis of the MRL is supported by necrosis and mild hepatic fatty changes seen in other acute- and intermediate-duration studies in rats (DeAngelo et al. 1986; Lake et al. 1984, 1986; Mann et al. 1985). Thyroid toxicity (decreased thyroxine levels and ultrastructural changes) was observed after rats were fed 2,000 mg/kg/day of di-*n*-octylphthalate in the diet for 3, 10, or 21 days (Hinton et al. 1986).

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

A table (2-l) and figure (2-l) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-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 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number IS), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 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 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q1*).

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

SAMPLE

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

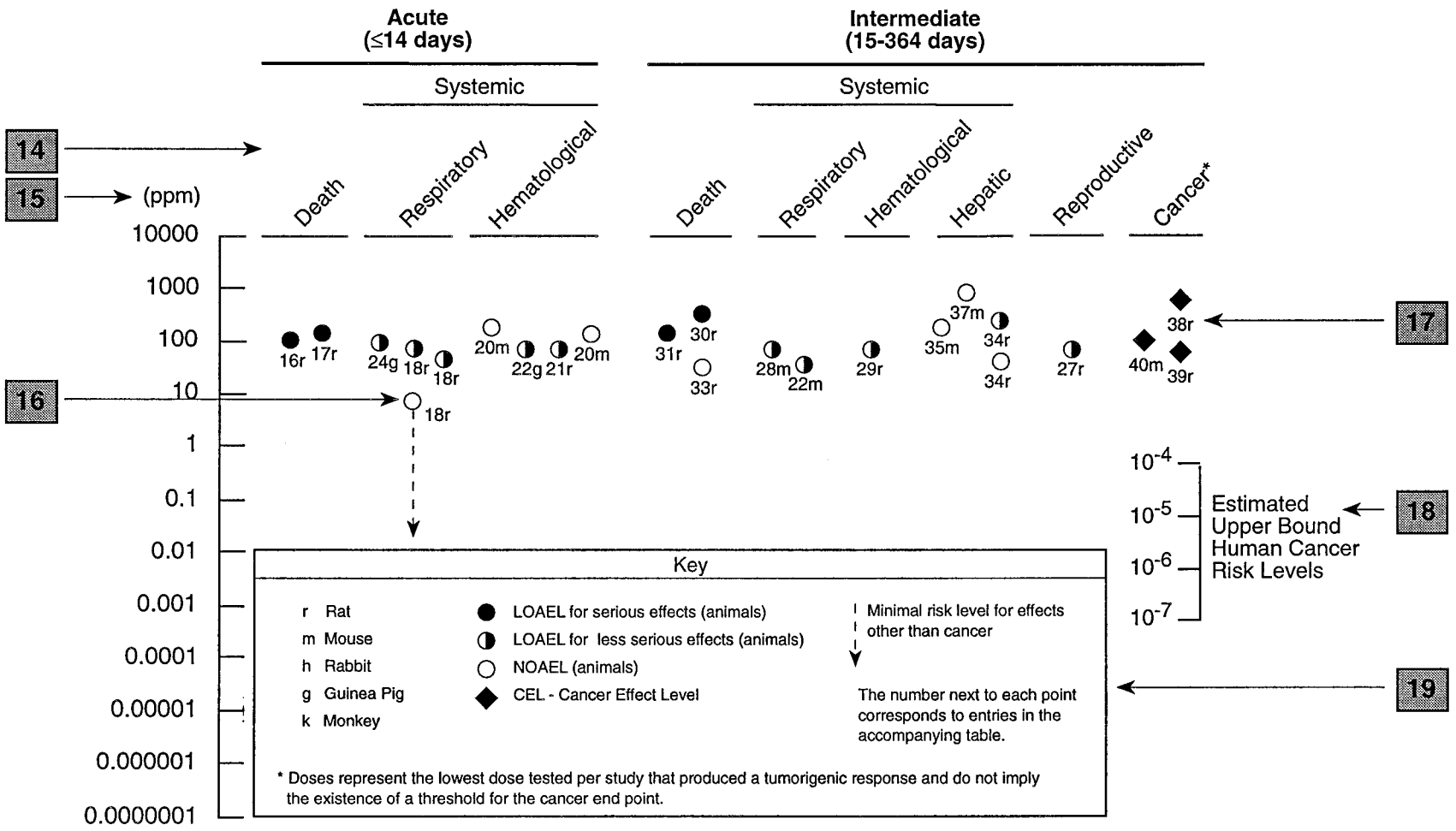
[a] The number corresponds to entries in Figure 2-1.

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 2.5)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.7, “Interactions with Other Substances,” and 2.8, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

APPENDIX B

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 C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
AML	acute myeloid leukemia
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BEI	Biological Exposure Index
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
Ci	curie
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
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
MA	trans,trans-muconic acid
mCi	millicurie
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NCE	normochromatic erythrocytes
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
PCE	polychromatic erythrocytes
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
UMDNJ	University of Medicine and Dentistry New Jersey
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
≈	approximately equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram