Toxicological Profile for

DI-n-BUTYLPHTHALATE

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

TP-90-10

TOXICOLOGICAL PROFILE FOR DI-N-BUTYL PHTHALATE

Prepared by:

Life Systems, Inc.
Under Subcontract to:

Clement Associates, Inc.
Under Contract No. 205-88-0608

Prepared for:

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

December 1990

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.

FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, on October 20, 1988, on October 26, 1989, and on October 17, 1990.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,

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

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

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by CERCLA, as amended.

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

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning significant health effects associated with exposure to the substance. The adequacy of information to determine a substance's health effects is described. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

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

William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about di-n-butyl phthalate and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). Di-n-butyl phthalate has been found at 47 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for di-n-butyl phthalate. As EPA evaluates more sites, the number of sites at which di-n-butyl phthalate is found may change. The information is important for you because di-n-butyl phthalate may cause harmful health effects and because these sites are potential or actual sources of human exposure to di-n-butyl phthalate.

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

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

1.1 WHAT IS DI-N-BUTYL PHTHALATE?

Di-n-butyl phthalate is an odorless and colorless oily liquid. It is a man-made chemical that is added to plastics and other chemical products. Di-n-butyl phthalate has been used to make soft plastics, carpet backing, paints, glue, insect repellents, hair spray, nail polish, and rocket fuel.

Di-n-butyl phthalate does not evaporate easily, but small amounts do enter into the air as a gas. Di-n-butyl phthalate also gets into air by attaching to dust particles. In air, di-n-butyl phthalate usually breaks down within a few days. Di-n-butyl phthalate does not dissolve easily in water, but can get into water by attaching to dirt particles. In water and soil, bacteria break down di-n-butyl phthalate. This may happen in a day, or may take up to a month. The length of time it takes

to break down di-n-butyl phthalate in soil or water depends on the kind of bacteria present and the temperature. Further information on the properties and uses of di-n-butyl phthalate and how it behaves in the environment may be found in Chapters 3, 4 and 5.

1.2 HOW MIGHT I BE EXPOSED TO DI-N-BUTYL PHTHALATE?

Because di-n-butyl phthalate has so many uses in modern society, it has become widespread in the environment, and most people are exposed to low levels in air, water and food. In most cases, the largest source of exposure is from food that contains di-n-butyl phthalate. Some di-n-butyl phthalate in food comes from the plastics used to package and store the food, and some of it comes from di-n-butyl phthalate taken up by fish, shellfish, or other foods. Levels of di-n-butyl phthalate in food have been found to range from around 50 to 500 parts per billion (ppb).

Another way you can be exposed is by breathing air containing di-n-butyl phthalate. Low levels (0.01 ppb) are present around the globe, and levels of 0.03 to 0.06 ppb are often found in city air. Higher levels can occur inside homes, especially when products containing di-n-butyl phthalate, such as nail polish, are used. Di-n-butyl phthalate is present in some drinking water supplies, usually at levels of around 0.1 to 0.2 ppb.

As discussed in Section 1.5 (below), the levels of di-n-butyl phthalate found in air, water, and food are usually low enough that they are not expected to cause any harmful effects. However, if you were exposed to higher-than-usual levels of di-n-butyl phthalate, this might be of concern. Exposure to high levels could occur at a number of places. For example, if you live near a factory that makes or uses di-n-butyl phthalate, you could be exposed if the factory allowed di-n-butyl phthalate to escape into the air that you breathe or into the water that you drink. If the factory spilled or disposed of any di-n-butyl phthalate on the ground, you could also be exposed by getting the soil on your skin. You could be exposed to elevated levels of di-n-butyl phthalate by these same ways if you live near a chemical waste site that has allowed di-n-butyl phthalate to escape into the environment. Di-n-butyl phthalate release into the air, water and soil is also of concern at garbage dumps and landfills. This is because large amounts of di-n-butyl phthalate-containing materials are thrown away at these sites, and the di-n-butyl phthalate can slowly come out of the products and get into air, water, or soil.

Further information on how you might be exposed to di-n-butyl phthalate is given in Chapter 5.

1.3 HOW CAN DI-N-BUTYL PHTHALATE ENTER AND LEAVE MY BODY?

If you eat or drink di-n-butyl phthalate in food or water, nearly all of the di-n-butyl phthalate rapidly enters your body through the digestive system. If you breathe air containing di-n-butyl phthalate, it is likely that most of what you breathe in enters your body through the lungs, but this has not been studied in detail. Di-n-butyl phthalate can also enter the body through skin, although this occurs rather slowly. Inside the body, di-n-butyl phthalate is changed into other chemicals. Most of these are quickly removed from the body in the urine. The rest are removed in the feces. Most of the di-n-butyl phthalate that enters the body is removed within 24 hours, and virtually all of it is gone by 48 hours after exposure. More information on how di-n-butyl phthalate enters and leaves the body is given in Chapter 2.

1.4 HOW CAN DI-N-BUTYL PHTHALATE AFFECT MY HEALTH?

Adverse effects on humans from exposure to di-n-butyl phthalate have not been reported. In animals, eating large amounts of di-n-butyl phthalate can affect their ability to reproduce. Di-n-butyl phthalate can cause death of unborn animals. In male animals, sperm production can decrease after eating large amounts of di-n-butyl phthalate. However, when exposure to di-n-butyl phthalate stops, sperm production seems to return to near normal levels. Exposure to high levels of di-n-butyl phthalate might cause similar effects in humans as in animals, but this is not known. There is no evidence that di-n-butyl phthalate causes cancer, but this has not been thoroughly studied.

Further information on the health effects of di-n-butyl phthalate in animals can be found in Chapter 2.

1.5 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Di-n-butyl phthalate appears to have relatively low toxicity, and large amounts are needed to cause injury. The levels of di-n-butyl phthalate which cause toxic effects in animals are about 10,000 times higher than the levels of di-n-butyl phthalate found in air, food or water. If you were to eat di-n-butyl phthalate at levels equal to those at which effects were seen in animals, about 1-2% of what you eat every day would have to be di-n-butyl phthalate. Large amounts of di-n-butyl phthalate repeatedly applied to the skin for a long time may also cause mild irritation.

Tables 1-1 through 1-4 show the relationship between exposure to di-n-butyl phthalate and known health effects. A Minimal Risk Level (MRL) is also included in Table 1-3. This MRL was derived from animal data for long-term exposure, as described in Chapter 2 and Table 2-2.

1. PUBLIC HEALTH STATEMENT

TABLE 1-1. Human Health Effects from Breathing Di-n-butyl Phthalate*

Short-term Exposure (less than or equal to 14 days)		
Levels in Air	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of humans to air containing specific levels of di-n-butyl phthalate are not known.
Long-term Exposure (greater than 14 days)		
Levels in Air	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of humans to air containing specific levels of di-n-butyl phthalate are not known.

*See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-2. Animal Health Effects from Breathing Di-n-butyl Phthalate

Short-term Exposure (less than or equal to 14 days)		
Levels in Air	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of animals to air containing specific levels of di-n-butyl phthalate are not known.
Long-term Exposure (greater than 14 days)		
Levels in Air (ppb)	Length of Exposure	Description of Effects*
4,400	6 months	Increased lung weight and decreased body weight gain in rats.

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

TABLE 1-3. Human Health Effects from Eating or Drinking Di-n-butyl Phthalate*

Short-term Exposure (less than or equal to 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of humans to food containing specific levels of di-n-butyl phthalate are not known.
Levels in Water		The health effects resulting from short-term exposure of humans to water containing specific levels of di-n-butyl phthalate are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppb)	Length of Exposure	Description of Effects
22,000	20 days	Minimal Risk Level (based on animal studies; see Section 1.5 for discussion).
Levels in Water		The health effects resulting from long-term exposure of humans to water containing specific levels of di-n-butyl phthalate are not known.

*See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-4. Animal Health Effects from Eating or Drinking Di-n-butyl Phthalate

Short-term Exposure (less than or equal to 14 days)		
Levels in Food (ppb)	Length of Exposure	Description of Effects*
19,000,000	8 days	Death in mice.
19,000,000	8 days	Death of unborn mice.
20,000,000	7 days	Decreased body weight in mice.
20,000,000	7 days	Decreased sperm production in rats.
Levels in Water		The health effects resulting from short-term exposure of animals to water containing specific levels of di-n-butyl phthalate are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food (ppb)	Length of Exposure	Description of Effects*
2,500,000	20 days	Decreased body weight of newly-born rats.
7,500,000	20 days	Death of unborn mice.
12,000,000	90 days	Death of unborn rats.
12,500,000	52 weeks	Death in rats.
16,000,000	18 days	Birth defects in mice.
Levels in Water		The health effects resulting from long-term exposure of animals to water containing specific levels of di-n-butyl phthalate are not known.

*These effects are listed at the lowest level at which they were first observed. They may also be seen at higher levels.

The MRL provides a basis for comparison to levels which people might encounter either in the air or in food or drinking water. If a person is exposed to di-n-butyl phthalate at an amount below the MRL, it is not expected that harmful health effects will occur. Because these levels are based only on information currently available, some uncertainty is always associated with them. Also, because the method for deriving MRLs does not use any information about cancer, a MRL does not imply anything about the presence, absence, or level of risk of cancer.

Additional information on the levels of exposure associated with harmful effects can be found in Chapter 2.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO DI-N-BUTYL PHTHALATE?

Tests are available that can detect di-n-butyl phthalate in blood and body tissues, and the major break-down products of di-n-butyl phthalate can be measured in urine. However, there is not enough information at present to use the results of such tests to predict the nature or severity of any health effects that may result from exposure to di-n-butyl phthalate. Since special equipment is needed, these tests cannot be performed routinely in your doctor's office. Further information on how di-n-butyl phthalate can be measured in exposed humans is presented in Chapters 2 and 6.

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

The federal government has developed regulatory standards and advisories to protect individuals from the potential health effects of di-n-butyl phthalate in the environment. The Environmental Protection Agency recommends that levels of di-n-butyl phthalate in water not exceed 34 parts per million (34,000 ppb). Any release of di-n-butyl phthalate to the environment in excess of 10 pounds must be reported to the federal government. The National Institute for Occupational Safety and Health (NIOSH) has established a limit of 850 parts per million (850,000 ppb) di-n-butyl phthalate in workplace air in order to protect the health of workers.

Additional information on governmental regulations regarding di-n-butyl phthalate can be found in Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your State Health or Environmental Department or:

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

This agency can also give you information on the location of the nearest occupational and environmental health clinics. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to di-n-butyl phthalate. Its purpose is to present levels of significant exposure for di-n-butyl phthalate based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of di-n-butyl phthalate and (2) a depiction of significant exposure levels associated with various adverse health effects.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each exposure route and duration (for which data exist) 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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies 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 on the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) are of interest to health professionals and citizens alike.

2. HEALTH EFFECTS

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1989a), uncertainties are associated with the techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of these procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

Table 2-1 and Figure 2-1 summarize the health effects observed in animals following inhalation exposure to di-n-butyl phthalate. These effects are discussed below.

2.2.1.1 Death

No studies were located regarding death in humans or animals following inhalation exposure to di-n-butyl phthalate.

2.2.1.2 Systemic Effects

Workers exposed to di-n-butyl phthalate for 0.5 to 19 years at concentrations of 1.7 to 66 mg/m^3 exhibited hypertension and hyperbilirubinemia at a frequency which increased with length of employment (Milkov et al. 1973). These workers were also exposed to other plasticizers, so the effects seen may not have been caused by di-n-butyl phthalate exposure.

Limited information on inhalation exposure in rats is available. Five days of exposure to 0.5 to 7 ppm di-n-butyl phthalate caused a dose-dependent decrease in the cytochrome P-450 content of the lungs of male rats (Walseth and Nilsen 1984). Rats exposed to 4.4 ppm di-n-butyl phthalate 6 hours per day for 6 months had decreased body weight gain and increased lung weight relative to body weight (Kawano 1980a). No effects on liver and kidney weight relative to body weight were found, and no effect was noted on hematocrit, hemoglobin, or red blood cell count (Kawano 1980a). Small fluctuations in several serum chemistry parameters were noted (serum enzymes, urea nitrogen, cholesterol), but these were not clearly dose- or time-dependent (Kawano 1980a).

TABLE 2-1. Levels of Significant Exposure to Di-n-butyl Phthalate - Inhalation

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Systemic							
1	Rat	5 d 6hr/d	Resp	0.5	2.5 (decr. cyto P-450)		Walseth and Nilsen 1984
INTERMEDIATE EXPOSURE							
Systemic							
2	Rat	3-6 mo 5d/wk 6hr/d	Resp	0.044	4.4[a] (incr. lung wt.)		Kawano 1980a
3	Rat	3-6 mo 5d/wk 6hr/d	Hepatic	4.4			Kawano 1980a
4	Rat	3-6 mo 5d/wk 6hr/d	Hemato	4.4			Kawano 1980a
5	Rat	3-6 mo 5d/wk 6hr/d	Other	0.044	4.4[a] (decr. wt. gain)		Kawano 1980a
6	Rat	3-6 mo 5d/wk 6hr/d	Renal	4.4			Kawano 1980a
7	Rat	3-6 mo 5d/wk 6hr/d	Resp	0.044	4.4 (increased lung weight)		Kawano 1980b
			Hemato	4.4			
			Hepatic	4.4			
			Renal	4.4			
			Other	0.044	4.4 (decreased weight gain)		

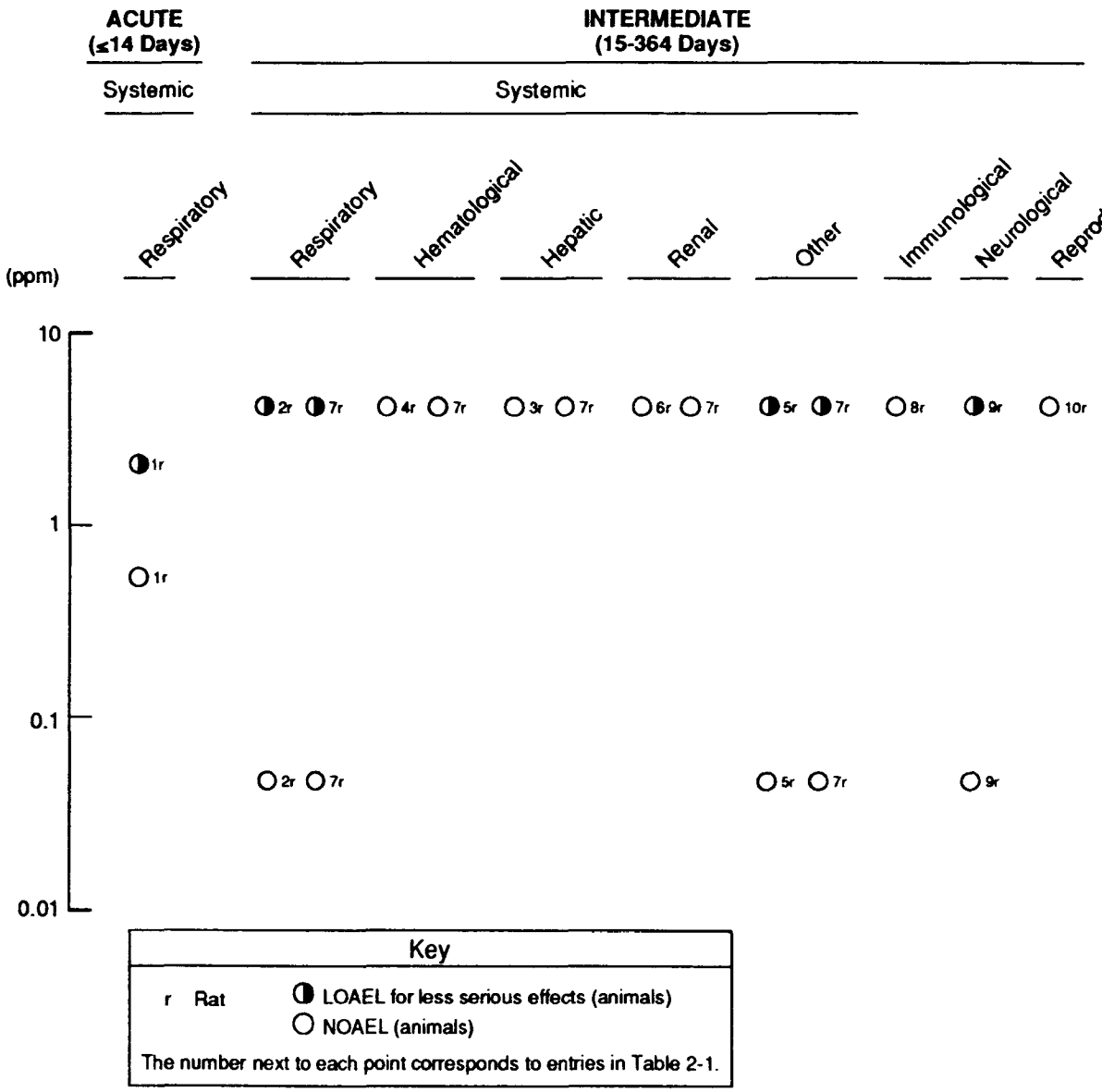
TABLE 2-1 (Continued)

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (ppm)	LOAEL (Effect) Less Serious (ppm)	LOAEL (Effect) Serious (ppm)	Reference
Immunological							
8	Rat	3-6 mo 5d/wk 6hr/d		4.4			Kawano 1980a
Neurological							
9	Rat	3-6 mo 5d/wk 6hr/d		0.044	4.4 (incr. brain wt.)		Kawano 1980a
Reproductive							
10	Rat	3-6 mo 5d/wk 6hr/d		4.4			Kawano 1980a

[a]Converted to 4,400 ppb for presentation in Table 1-2.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; mo = month; hr = hour; d = day; resp = respiratory; incr. = increased; wt. = weight; decr. = decreased.

FIGURE 2-1. Levels of Significant Exposure to Di-n-butyl Phthalate – Inhalation



No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, or dermal/ocular effects in animals following inhalation exposure to di-n-butyl phthalate.

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans following inhalation exposure to di-n-butyl phthalate. Small fluctuations in white cell counts and percent neutrophiles were found in rats exposed to 0.044 or 4.4 ppm di-n-butyl phthalate 6 hours per day for 3 or 6 months, but the changes were not dose- or time-dependent (Kawano 1980a), and do not appear to be clinically significant.

2.2.1.4 Neurological Effects

Workers exposed to di-n-butyl phthalate for 0.5 to 19 years at concentrations of 1.7 to 66 mg/m^3 experienced neurological symptoms (pain, numbness, spasms, weakness) and exhibited reflex disturbances, elevated thresholds for pain sensitivity and olfactory stimulation, and depression of vestibular function (Milkov et al. 1973). The frequency and severity of these effects increased with increased duration of exposure. The workers were also exposed to other plasticizers, so these neurological effects may not have been caused by di-n-butyl phthalate exposure.

In rats, a statistically significant increase in brain weight as a percent of body weight was observed following exposure to 4.4 ppm di-n-butyl phthalate for six months (Kawano 1980a). However, a significant decrease in body weight gain was reported for this dose group, and the absolute brain weight increase was small (1.58 g vs. 1.47 g in controls).

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals following inhalation exposure to di-n-butyl phthalate.

2.2.1.6 Reproductive Effects

No studies were located regarding reproductive effects in humans following inhalation exposure to di-n-butyl phthalate. In rats, exposure to 0.044 or 4.4 pm 6 hours per day for 3 or 6 months caused no changes in relative testicular weight (Kawano 1980a).

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals following inhalation exposure to di-n-butyl phthalate.

2.2.1.8 Cancer

No studies were located regarding cancer effects in humans or animals following inhalation exposure to di-n-butyl phthalate.

2.2.2 Oral Exposure

Table 2-2 and Figure 2-2 summarize the health effects observed following oral exposure of animals to di-n-butyl phthalate. These effects are discussed below.

2.2.2.1 Death

No studies were located regarding death in humans following oral exposure to di-n-butyl phthalate.

Di-n-butyl phthalate has low acute toxicity in animals. Single doses of 8,000 mg/kg killed 4 of 9 rats in one study (Smith 1953), but other studies indicate the acute oral LD_{50} in rats and mice is in excess of 20,000 mg/kg (Hardin et al. 1987; White et al. 1983). The cause of death in these studies was not reported. In mice, an LD_{10} of 2,500 mg/kg was reported by Hardin et al. (1987).

In a 52 week study in rats, half of the animals given 625 mg/kg/day in feed died during the first week of the study. Because those animals that survived the first week also survived to the termination of the study and exhibited no pathology, the observed deaths may not have been related to di-n-butyl phthalate exposure. No deaths were observed at 125 mg/kg/day (Smith 1953).

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

2.2.2.2 Systemic Effects

Hematological Effects. Di-n-butyl phthalate has little or no effect on the hematological system of animals. Biochemical parameters and histopathological evaluation of the spleen of rats showed no effects at doses up to 1,200 mg/kg/day (Nikonorow et al. 1973; Smith 1953). Increased absolute and relative spleen weight was observed in rats at a dose of 2,500 mg/kg/day (Murakami et al. 1986a, 1986b), but without additional information on histopathological changes and evaluation of hematological parameters, the significance of this isolated finding cannot be determined.

TABLE 2-2. Levels of Significant Exposure to Di-n-butyl Phthalate - Oral

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/d)	LOAEL (Effect) Less Serious (mg/kg/d)	LOAEL (Effect) Serious (mg/kg/d)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(G)	1 d		6000		10000 (2/10 deaths)	White et al. 1983
2	Rat	(G)	1 d		4000		8000 (4/9 deaths)	Smith 1953
3	Mouse	(G)	8 d Gd6-13 1x/d				2500[a] (LD10)	Hardin et al. 1987
Systemic								
4	Rat	(G)	1 d 1x/d	Resp	0.044	4.4 (increased lung weight)		Kawano 1980b
				Hemato	4.4			
				Hepatic	4.4			
				Renal	4.4			
				Other	0.044	4.4 (decreased weight gain)		
5	Rat	(G)	9 d 1x/d	Other	2000			Gray et al. 1982
6	Rat	(F)	7 d	Hepatic		1000 (decr. zinc conc.)		Oishi and Hiraga 1980b
7	Rat	(G)	5 d 1x/d	Resp	278			Walseth and Nilsen 1986
8	Rat	(G)	1 d	Other	4000	8000 (decr. body wt.)		Smith 1953
9	Rat	(F)	7 d	Other	1000			Oishi and Hiraga 1980b
10	Rat	(F)	7 d	Hepatic		1000 (incr. liver enz. act.)		Kawashima et al. 1983
11	Gn Pig	(G)	7 d 1x/d	Other	2000			Gray et al. 1982

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/d)	LOAEL (Effect) Less Serious (mg/kg/d)	LOAEL (Effect) Serious (mg/kg/d)	Reference
12	Mouse	(F)	7 d	Other		2600[b] (decr. body wt.)		Oishi and Hiraga 1980a
13	Mouse	(F)	7 d	Hepatic		2600 (incr. liver wt.)		Oishi and Hiraga 1980a
14	Mouse	(F)	7 d	Renal		2600 (decr. kidney wt.)		Oishi and Hiraga 1980a
15	Mouse	(G)	9 d 1x/d	Other	2000			Gray et al. 1982
16	Hamster	(G)	9 d 1x/d	Other	2000			Gray et al. 1982
Developmental								
17	Mouse	(G)	8 d Gd6-13 1x/d				2500[a] (no viable litters)	Hardin et al. 1987
Reproductive								
18	Rat	(G)	7 d 1x/d				2400 (histopath damage, decr. testis wt.)	Tanino et al. 1987
19	Rat	(G)	9 d 1x/d				2000 (severe testic. lesion, decr. testis wt.)	Gray et al. 1982
20	Rat	(F)	7 d				1000[b] (decr. spermatocytes, testis wt., zinc conc.; incr. testosterone level)	Oishi and Hiraga 1980b
21	Rat	(G)	4 d 1x/d				1000 (decr. testis wt.)	Cater et al. 1977
22	Gn Pig	(G)	7 d 1x/d				2000 (severe testic. lesion, decr. testis wt.)	Gray et al. 1982

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/d)	LOAEL (Effect) Less Serious (mg/kg/d)	LOAEL (Effect) Serious (mg/kg/d)	Reference
23	Mouse	(F)	7 d				2600 (incr. testis wt.)	Oishi and Hiraga 1980a
24	Mouse	(G)	9 d 1x/d				2000 (mild testic. lesion, decr. testis wt.)	Gray et al. 1982
25	Hamster	(G)	9 d 1x/d		2000			Gray et al. 1982
INTERMEDIATE EXPOSURE								
Death								
26	Rat	(F)	52 wk		125		625[c]	Smith 1953
Systemic								
27	Rat	(F)	12 mo	Hemato	62			Nikonorow et al. 1973
28	Rat	(F)	34-36 d	Other		250 (decr. body wt.)		Murakami et al. 1986a
29	Rat	(F)	21 d	Other		348 (decr. plasma cholesterol)		Bell 1982
30	Rat	(G)	90 d 1x/d	Renal	1200			Nikonorow et al. 1973
31	Rat	(G)	90 d 1x/d	Hepatic	120	1200 (incr. liver wt.)		Nikonorow et al. 1973
32	Rat	(F)	21 d	Hepatic		348 (incr. liver wt.)		Bell 1982
33	Rat	(F)	52 wk	Hemato	625			Smith 1953
34	Rat	(F)	34-36 d	Hepatic			250 (liver necrosis)	Murakami et al. 1986a
35	Rat	(G)	90 d 1x/d	Hemato	1200			Nikonorow et al. 1973

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/d)	LOAEL (Effect) Less Serious (mg/kg/d)	LOAEL (Effect) Serious (mg/kg/d)	Reference
36	Rat	(F)	35-45 d	Other		2500 (decr. body wt.)		Murakami et al. 1986b
37	Rat	(F)	21 d	Hepatic		628 (incr. liver wt.)		BIBRA 1986
38	Rat	(F)	12 mo	Other	62			Nikonorow et al. 1973
39	Rat	(F)	12 mo	Hepatic	62			Nikonorow et al. 1973
40	Rat	(F)	21 d	Renal	628	1248 (incr. kidney wt.)		BIBRA 1986
41	Rat	(F)	35-45 d	Hemato		2500 (incr. spleen wt.)		Murakami et al. 1986b
42	Rat	(F)	12 mo	Renal	62			Nikonorow et al. 1973
43	Rat	(F)	35-45 d	Hepatic		2500 (decr. mitoch. oxidation)		Murakami et al. 1986b
44	Mouse	(F)	105 d	Hepatic	1300			Lamb et al. 1987
45	Mouse	(F)	126 d	Hepatic	390	1300 (incr. liver wt.)		Reel et al. 1984
46	Mouse	(F)	126 d	Other	390	1300 (decr. body wt.-males)		Reel et al. 1984
47	Mouse	(F)	105 d	Other	390	1300 (decr. body wt.)		Lamb et al. 1987
48	Mouse	(F)	18 d	Other	660		2100 (decr. body wt.)	Shiota and Nishimura 1982
49	Mouse	(F)	21 d	Other	628	1248 (decr. body wt.)		BIBRA 1986
Developmental								
50	Rat	(F)	48 d Gd0-Ld28		62.5[d]	125[e] (decr. pup wt.)		Killinger et al. 1988a
51	Rat	(G)	90 d		120		600[f] (incr. no. of resorptions)	Nikonorow et al. 1973

TABLE 2-2 (Continued)

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/d)	LOAEL (Effect) Less Serious (mg/kg/d)	LOAEL (Effect) Serious (mg/kg/d)	Reference
52	Mouse	(F)	48 d Gd0-Ld28		650		975[g] (fetal death)	Killinger et al. 1988b
53	Mouse	(F)	18 d Gd0-18		660		2100[h] (malformations)	Shiota and Nishimura 1982
Reproductive								
54	Rat	(F)	34-36 d		250		2500 (decr. testis wt.)	Murakami et al. 1986a
55	Rat	(F)	48 d Gd0-Ld28				1000 (no live pups)	Killinger et al. 1988a
56	Rat	(F)	35-45 d				2500 (decr. testis wt.)	Murakami et al. 1986b
57	Rat	(F)	21 d		1248		2131 (testic. atrophy)	BIBRA 1986
58	Mouse	(F)	105 d		390		1300 (decr. no. litters and live pups)	Lamb et al. 1987
59	Mouse	(F)	48 d Gd0-Ld28				2600 (no live pups)	Killinger et al. 1988b

[a]Converted to an equivalent concentration of 19,000,000 ppb in food for presentation in Table 1-4.
[b]Converted to an equivalent concentration of 20,000,000 ppb in food for presentation in Table 1-4.
[c]Converted to an equivalent concentration of 12,500,000 ppb in food for presentation in Table 1-4.
[d]Used to derive intermediate oral MRL; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability), resulting in an MRL of 0.62 mg/kg/day. This MRL has been converted to an equivalent concentration in food (22,000 ppb) for presentation in Table 1-3.
[e]Converted to an equivalent concentration of 2,500,000 ppb in food for presentation in Table 1-4.
[f]Converted to an equivalent concentration of 12,000,000 ppb in food for presentation in Table 1-4.
[g]Converted to an equivalent concentration of 7,500,000 ppb in food for presentation in Table 1-4.
[h]Converted to an equivalent concentration of 16,000,000 ppb in food for presentation in Table 1-4.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; mg = milligram; kg = kilogram; d = day; (G) = gavage; LD10 = lethal dose, 10% mortality; Gd = gestation day; Ld = lactation day; 1x = one time; (F) = food; decr. = decreased; conc. = concentration; incr. = increased; enz. act. = enzyme activity; Resp = respiratory; wt. = weight; histopath = histopathological; testic = testicular; Gn = guinea pig; wk = week; mo = month; Hemato = hematological; mitoch. = mitochondrial; no. = number.

FIGURE 2-2. Levels of Significant Exposure to Di-n-butyl Phthalate – Oral

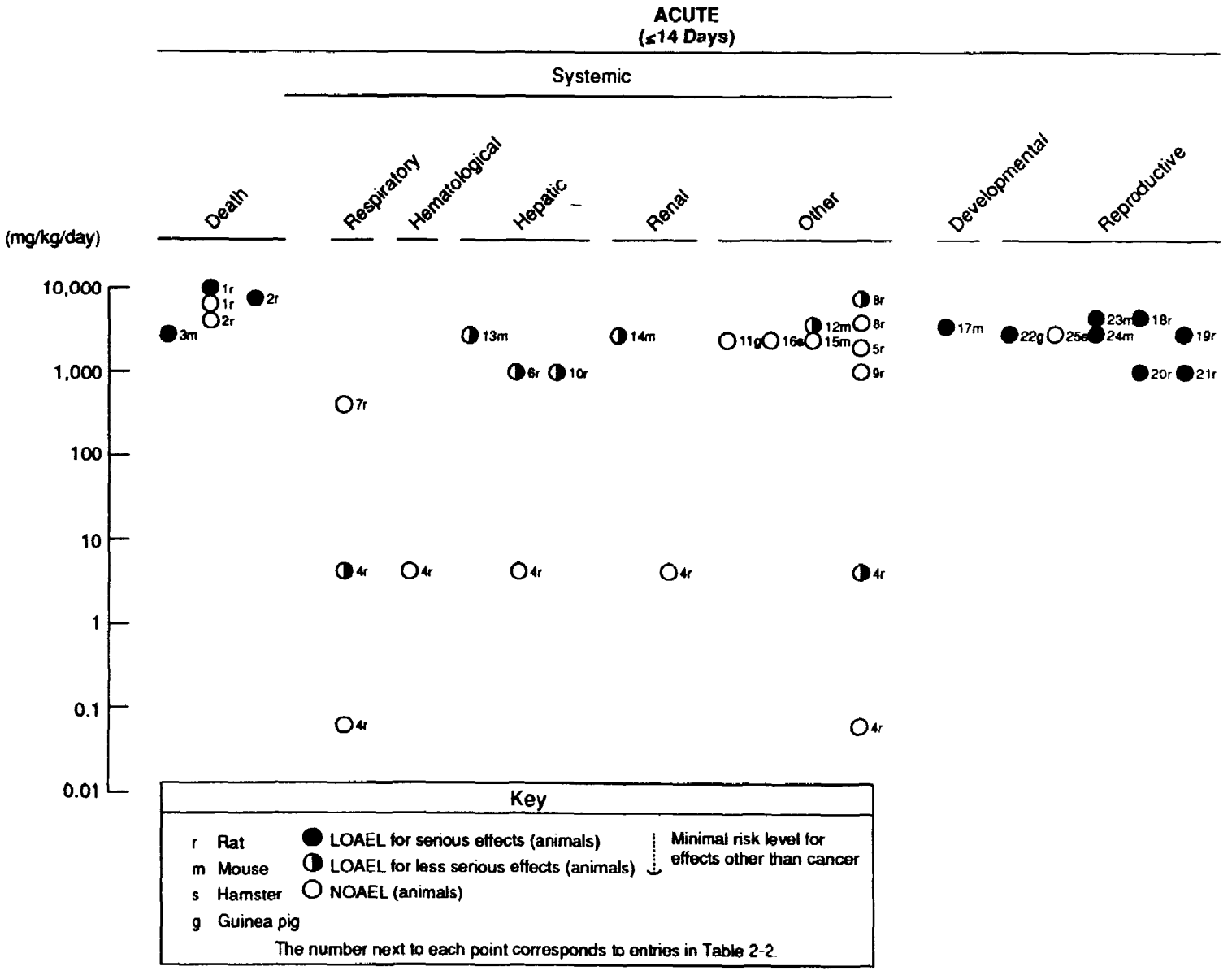
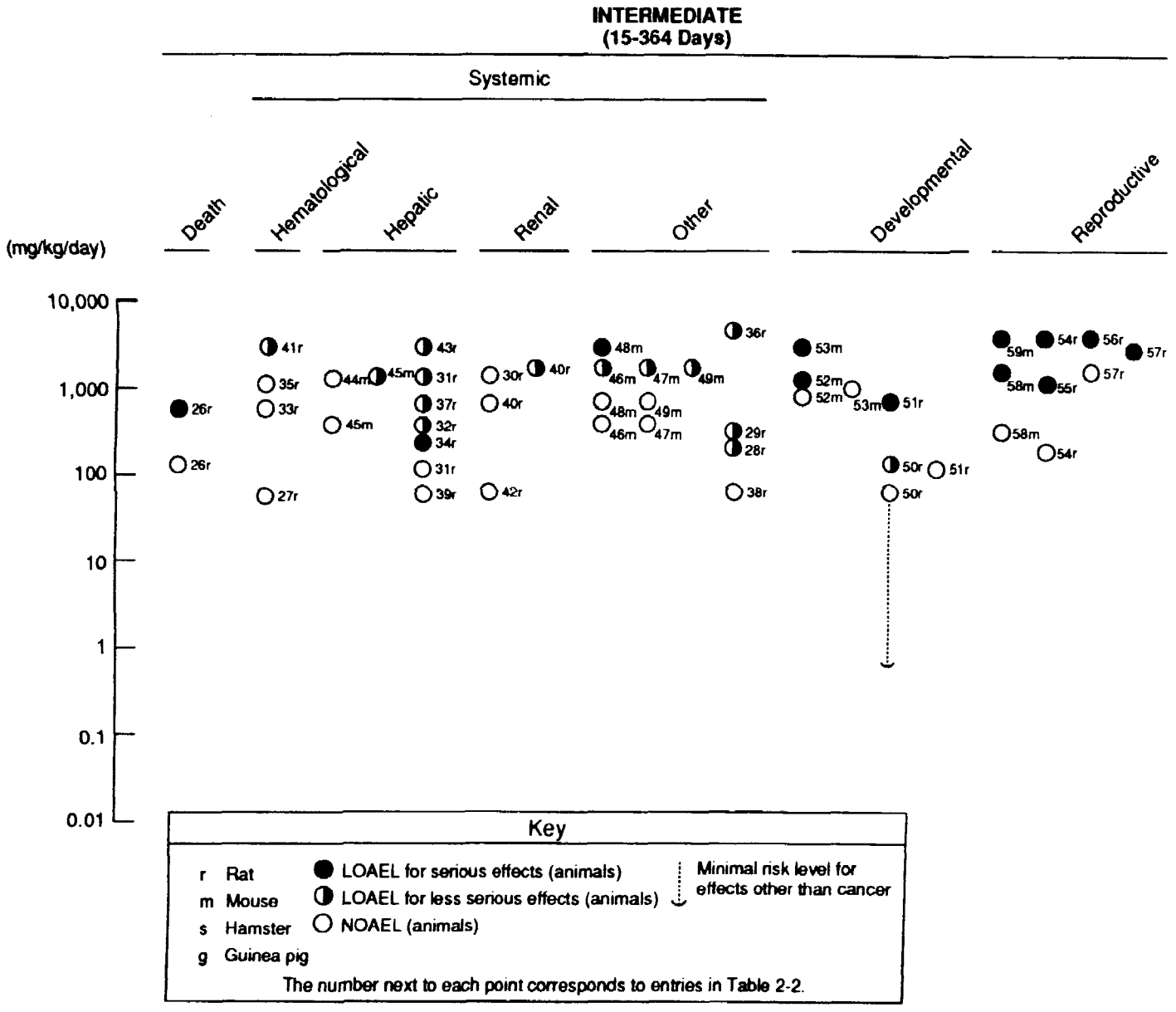


FIGURE 2-2 (Continued)



2. HEALTH EFFECTS

Hepatic Effects. In animals, minimal effects on the liver are observed after acute exposure to di-n-butyl phthalate. Increased absolute liver weight was observed in rats and mice given di-n-butyl phthalate at 2% in the diet (1,000 to 2,600 mg/kg/day) for 7 days (Oishi and Hiraga 1980a, 1980b), and increased liver weight relative to body weight in animals was observed in several studies with di-n-butyl phthalate at doses of 348 mg/kg/day and higher for 21 days or more (Bell 1982; BIBRA 1986; Murakami et al. 1986a, 1986b; Nikonorow et al. 1973). In these studies, the increases in relative liver weight may simply reflect body weight decreases caused by di-n-butyl phthalate in those animals.

Slight but statistically significant increases in microsomal enzyme activity levels were observed in the livers of rats given di-n-butyl phthalate by gavage for 5 days at doses of 2.8 and 27.8 mg/kg/day, but not at 278 mg/kg/day (Walseth and Nilsen 1986). Why increased enzyme activity was observed at the lower doses but not at the high dose was not evident. The authors considered di-n-butyl phthalate to be a weak inducer of microsomal enzymes. Increased microsomal enzyme activity was observed in the livers of rats exposed to 1,000 mg/kg/day in the diet for 7 days (Kawashima et al. 1983).

Longer exposure to di-n-butyl phthalate was found to interfere with mitochondrial respiration. Mitochondrial respiration was inhibited in rats fed di-n-butyl phthalate at 2,500 mg/kg/day for 35 days (Murakami et al. 1986b). Evaluation of liver tissue by electron microscopy revealed an increase in the number of mitochondria, suggesting that the organ is compensating for the inhibitory effects of the di-n-butyl phthalate on mitochondrial function (Murakami et al. 1986a). Liver necrosis was noted at doses of 250 mg/kg/day and higher, an effect possibly related to the effects of di-n-butyl phthalate on liver mitochondria (Murakami et al. 1986a). Other studies using higher doses have found no liver necrosis (BIBRA 1986, Nikonorow et al. 1973). No explanation for the discrepant results is evident.

Proliferation of peroxisomes and increases in peroxisomal enzymes have been reported in rat liver cells by several investigators (BIBRA 1986; Murakami et al. 1986a) at doses of 2,131 mg/kg/day for 21 days or more. This response may contribute to the increase in liver weight discussed above, especially in males (Murakami et al. 1986a, 1986b).

Renal Effects. Oral exposure to di-n-butyl phthalate has been reported to cause decreased kidney weight after 7 days of exposure of mice to 2,600 mg/kg/day (Oishi and Hiraga 1980a) and increased kidney weight after 21 days of exposure of rats to 1,248 mg/kg/day (BIBRA 1986). No histopathologic lesions of the kidney have been observed in

rats exposed to di-n-butyl phthalate (BIBRA 1986; Nikonorow et al. 1973).

Other Systemic Effects. No studies were located regarding respiratory, cardiovascular, gastrointestinal, musculoskeletal, or dermal/ocular effects in humans or animals following ingestion of di-n-butyl phthalate. Several studies have evaluated the effect of oral exposure of animals to di-n-butyl phthalate on body weight (BIBRA 1986; Gray et al. 1982; Lamb et al. 1987; Murakami et al. 1986, 1986b; Nikonorow et al. 1973; Oishi and Hiraga 1980a; Reel et al. 1984; Smith 1953). Body weight changes are generally insensitive indicators of toxicity, and effects on testes are often found at doses causing no change in body weights (Gray et al. 1982; Oishi and Hiraga 1980b).

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

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following oral exposure to di-n-butyl phthalate.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals following oral exposure to di-n-butyl phthalate.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to di-n-butyl phthalate.

Di-n-butyl phthalate has been demonstrated to be toxic to fetuses in a number of animal studies (Hardin 1987; Killinger et al. 1988a,b; Nikonorow et al. 1973; Shiota and Nishimura 1982). Administration of di-n-butyl phthalate for 8 days at a dose of 2,500 mg/kg/day to pregnant mice resulted in the deaths of 10% of treated animals and no viable litters among the surviving females (Hardin et al. 1987). Oral doses of 600 mg/kg/day resulted in an increased number of resorptions when di-n-butyl phthalate was administered to rats during pregnancy. If di-n-butyl phthalate was given prior to mating, but discontinued on the day of conception, no fetotoxic effects were noted (Nikonorow et al. 1973). Offspring of pregnant rats fed 2,500 ppm or more di-n-butyl phthalate (125 mg/kg/day) for 48 days experienced decreased weight gain

(Killinger et al. 1988a). Pregnant mice fed 7,500 ppm or more for 28 days (975 mg/kg/day) had fewer live-born pups than controls (Killinger et al. 1988b). No maternal toxicity was noted in either study.

Limited data suggest that di-n-butyl phthalate may be teratogenic. Mice given di-n-butyl phthalate in the diet on days 0-18 of gestation and sacrificed on day 18 of gestation showed a borderline increase in fetal neural tube defects (exencephaly and myeloschisis) (Shiota and Nishimura 1982). The LOAEL for these malformations was 2,100 mg/kg/day and the NOAEL for malformations was 660 mg/kg/day.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. Based on the no effect level of 62.5 mg/kg/day in rats reported by Killinger et al. (1988a), an intermediate oral MRL of 0.62 mg/kg/day was calculated as described in footnote d in Table 2-2.

2.2.2.6 Reproductive Effects

A weak negative correlation was found between sperm density and di-n-butyl phthalate concentration in semen from male university students (Murature et al. 1987). No other studies were located regarding reproductive effects in humans following oral exposure to di-n-butyl phthalate.

Oral exposure to di-n-butyl phthalate has adverse effects on the male reproductive system in several animal species (rats, mice and guinea pigs). Oral exposure of male rats for up to 34 days at doses up to 2,500 mg/kg/day resulted in decreased testicular weight, atrophy of the seminiferous tubules, and decreased sperm counts (BIBRA 1986; Cater et al. 1977; Gray et al. 1982; Murakami et al. 1986a, 1986b; Oishi and Hiraga 1980b; Tanino et al. 1987). In rats, decreased spermatogenesis and testes weight were observed as early as 7 days after initiation of dosing with 1,000 mg/kg/day (Oishi and Hiraga 1980b).

Species differences are evident. While severe seminiferous tubular atrophy was observed in rats and guinea pigs at 2,000 mg/kg/day for 7 to 9 days, only focal atrophy was reported in mice at the same dose and no effects on the testes were seen in Syrian hamsters (Gray et al. 1982). This difference may be related to the greater ability of hamsters than other species to conjugate the primary metabolite of di-n-butyl phthalate (see Section 2.3.3.2).

The testicular effects of acute exposure of rats to di-n-butyl phthalate appear to be at least in part reversible. Tanino et al. (1987) showed that two weeks after discontinuation of the administration

of di-n-butyl phthalate (2,400 mg/kg/day for 7 days), some regeneration of seminiferous tubules had occurred. Three weeks after treatment ceased, active spermatogenesis was observed in almost all tubules. However, vacuolation of germinal epithelium and decreased number of sperm were still evident.

Testicular effects of di-n-butyl phthalate may be associated with the effects of di-n-butyl phthalate on the metabolism of zinc. Zinc is an essential element for the development of testes and administration of di-n-butyl phthalate increases the urinary excretion of zinc and decreases the zinc content of the testes of rats (Cater et al. 1977; Oishi and Hiraga 1980a). Administration of zinc to young male rats given 1,000 mg/kg/day di-n-butyl phthalate showed substantial protection against the testicular injury produced by di-n-butyl phthalate (Cater et al. 1977).

High doses of di-n-butyl phthalate also appear to have an adverse effect on reproduction in female animals. Pregnant rats or mice fed 20,000 ppm of di-n-butyl phthalate in the diet (equivalent to doses of 1,000 and 2,600 mg/kg/day, respectively) during gestation experienced complete reproductive failure, possibly due to toxic effects on the fetus (Killinger et al. 1988a, 1988b). No NOAEL for reproductive toxicity was established in these studies becauses decreases in fertility parameters seen at lower doses may have been related to fetal toxicity. Exposure of male and female mice to 1,300 mg/kg/day in the diet for 98 days resulted in a reduced number of litters per mating pair, fewer live pups per litter (possibly due to increased fetal mortality), and lower proportion of pups born alive (Lamb et al. 1987). No effects on reproduction were seen at 390 mg/kg/day. Crossover mating studies in which exposed females were mated with control males, and vice versa, showed that the effects on reproduction were associated with the female mice. The doses administered in the study appear to be below those which cause effects on reproductive organs in male mice. Gross and microscopic evaluation of reproductive organs of males in this study showed no adverse effects (Reel et al. 1984).

The highest NOAEL and all reliable LOAEL values for reproductive effects are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects of di-n-butyl phthalate in humans or animals after oral exposure to di-n-butyl phthalate.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects of di-n-butyl phthalate in humans after oral exposure to di-n-butyl phthalate. Rats exposed for 15 to 21 months to doses of 100 to 500 mg/kg/day were reported not to develop cancer, but no details of the study or the examination for tumors were provided (Krauskopf 1973). No other studies on the carcinogenic effects of chronic ingestion of di-n-butyl phthalate were located. An on-going study of the carcinogenicity of di-n-butyl phthalate is listed in Section 2.8.3.

2.2.3 Dermal Exposure

Available data on the effects of dermal exposure to di-n-butyl phthalate are presented in Table 2-3. These studies are discussed below.

2.2.3.1 Death

No studies were located regarding death in humans following dermal exposure to di-n-butyl phthalate.

The subchronic (90-day) dermal LD_{50} in rabbits has been reported to be greater than 4,200 mg/kg/day (Lehman 1955).

2.2.3.2 Systemic Effects

Renal Effects. No information concerning renal effects in humans following dermal exposure to di-n-butyl phthalate was located. Histological evidence of slight kidney damage was noted in rabbits after 90 days of dermal application of 4,200 mg/kg/day (Lehman 1955). No details about the study or specifics about the type of kidney damage were given. In this study, a NOAEL of 2,100 mg/kg/day was identified.

Dermal/Ocular Effects. Some cosmetic preparations containing di-n-butyl phthalate cause slight irritation to human skin (Cosmetic Ingredient Review Panel 1985). A single dermal application of 520 mg/kg/day of di-n-butyl phthalate was reported to be slightly irritating to skin and "quite irritating" to mucous membranes of rabbits (Lehman 1955). In a 90-day study, doses up to 4,200 mg/kg/day were described as slightly irritating, and slight dermatitis was reported. No data were presented, and the no-effect level was not given.

Other Systemic Effects. *No studies were located regarding* respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal or hepatic effects in humans or animals following dermal exposure to di-n-butyl phthalate.

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-3.

2.2.3.3 Immunological Effects

Di-n-butyl phthalate does not appear to be a skin sensitizer. A variety of cosmetic materials (e.g., deodorants, nail polish) containing 4.5% to 9% di-n-butyl phthalate were not skin sensitizers when tested on 50 to 250 individuals per sample (Cosmetic Ingredient Review Committee 1985). In a 90-day study in rabbits, there was no indication that di-n-butyl phthalate was a skin sensitizer (Lehman 1955).

No studies were located regarding the following health effects in humans or experimental animals after dermal exposure to di-n-butyl phthalate.

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding absorption in humans after inhalation exposure to di-n-butyl phthalate. The relatively low concentration of di-n-butyl phthalate found in the lungs of rats exposed to 4.4 ppm of di-n-butyl phthalate for up to 6 months was suggested to indicate rapid absorption (Kawano 1980b). However, no metabolites were measured in this study, and so the lack of accumulation could be due to lung metabolism rather than absorption.

2.3.1.2 Oral Exposure

No studies were located regarding absorption in humans after oral exposure to di-n-butyl phthalate.

TABLE 2-3. Levels of Significant Exposure to Di-n-butyl Phthalate - Dermal

Species	Exposure Frequency/ Duration	Effect	NOAEL (mg/kg/d)	LOAEL (Effect) Less Serious (mg/kg/d)	LOAEL (Effect) Serious (mg/kg/d)	Reference
ACUTE EXPOSURE						
Systemic						
Rabbit	1x	Derm/Oc		520 (slightly irritated)		Lehman 1955
INTERMEDIATE EXPOSURE						
Death						
Rabbit	90 d				4200 (LD 50)	Lehman 1955
Systemic						
Rabbit	90 d 1x/d	Renal	2100	4200 (kidney damage)		Lehman 1955

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; mg = milligram; kg = kilogram; d = day; 1x = one time; Derm/Oc = Dermal/Ocular; LD_{50} = lethal dose, 50% mortality.

2. HEALTH EFFECTS

Studies in laboratory animals indicate that di-n-butyl phthalate is rapidly and extensively absorbed by the oral route. Extensive absorption is indicated by the fact that in rats 63 to 97% of an orally administered dose was accounted for in the urine within 24 hours after dosing (Foster et al. 1982; Tanaka et al. 1978; Williams and Blanchfield 1975). Forty-eight hours after dosing, 85 to 100% of an oral dose of ^{14}C-di-n-butyl phthalate was excreted in the urine (Tanaka et al. 1978; Williams and Blanchfield 1975). Similar results were obtained in hamsters, where 79% of an orally administered dose of ^{14}C-di-n-butyl phthalate was excreted in the urine within 24 hours (Foster et al. 1982). In vitro studies indicate that a metabolite of di-n-butyl phthalate, monobutyl phthalate, is probably the main form absorbed through the intestine (Lake et al. 1977; Takahashi and Tanaka 1989).

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans after dermal exposure to di-n-butyl phthalate, although in vitro studies using human skin indicate that slow absorption by this route might occur (Scott et al. 1987).

In rats, 10 to 12% of a dermal dose was excreted in the urine each day for several days, reaching a total of 60% after 1 week (Elsisi et al. 1989). These data suggest that di-n-butyl phthalate is reasonably well absorbed at a constant rate across the skin.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans after inhalation exposure to di-n-butyl phthalate.

In rats exposed to di-n-butyl phthalate by inhalation for 3 or 6 months, di-n-butyl phthalate was detected in all organs examined from rats exposed at 4.4 ppm (Kawano 1980b). The highest concentrations were found in brain, followed by lung, kidney, testicles, and liver (Kawano 1980b). Organ concentrations varied considerably between rats. At exposure to 0.044 ppm, di-n-butyl phthalate was consistently detected only in brains of exposed rats (Kawano 1980b).

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to di-n-butyl phthalate.

Studies in rats on the distribution of ^{14}C-labeled di-n-butyl phthalate indicate that it is distributed throughout the body and that

no significant retention occurs in any organ (Tanaka et al. 1978; Williams and Blanchfield 1975). Evaluation of tissues for ^{14}C at intervals from 4 to 48 hours after dosing showed no accumulation. At all of the time points evaluated, no organ contained more than 0.7% of the administered dose (Williams and Blanchfield 1975). Even when rats were fed 0.1% di-n-butyl phthalate in the diet for up to 12 weeks, no accumulation in any organs was observed (Williams and Blanchfield 1975).

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans following dermal exposure to di-n-butyl phthalate.

A study in rats indicated that there was little or no accumulation of di-n-butyl phthalate in the body 7 days after a single dermal application of 44 mg/kg of ^{14}C-labeled di-n-butyl phthalate (Elsisi et al. 1989). Though approximately 65% of the dose had been absorbed and eliminated, only small amounts were found in tissues. Of the administered dose, 1.4% was in the skin, 1.1% in muscle, and 0.41% in adipose tissue. All other tissues combined contained less than 0.5% of the dose. About 33% of the dose remained at the site of application.

2.3.3 Metabolism

2.3.3.1 Inhalation Exposure

No studies were located regarding metabolism in humans or animals following inhalation exposure to di-n-butyl phthalate.

2.3.3.2 Oral Exposure

No studies were located regarding di-n-butyl phthalate metabolism in humans. Studies in animals indicate that metabolism of di-n-butyl phthalate proceeds mainly by hydrolysis of one butyl ester bond to yield monobutyl phthalate (MBP). The product that appears in the urine is mainly MBP conjugated with glucuronic acid, with lower levels of unconjugated MBP, various oxidation products of MBP, and a small amount of the free phthalic acid (Figure 2-3) (Albro and Moore 1974; Foster et al. 1982; Kawano 1980b; Tanaka et al. 1978; Williams and Blanchfield 1975).

Species differences in the excretion of conjugated and unconjugated di-n-butyl phthalate in the urine of rats and hamsters have been identified by Foster et al. (1982). Rats excreted a larger proportion (14%) of the administered dose as unconjugated MBP than hamsters, in

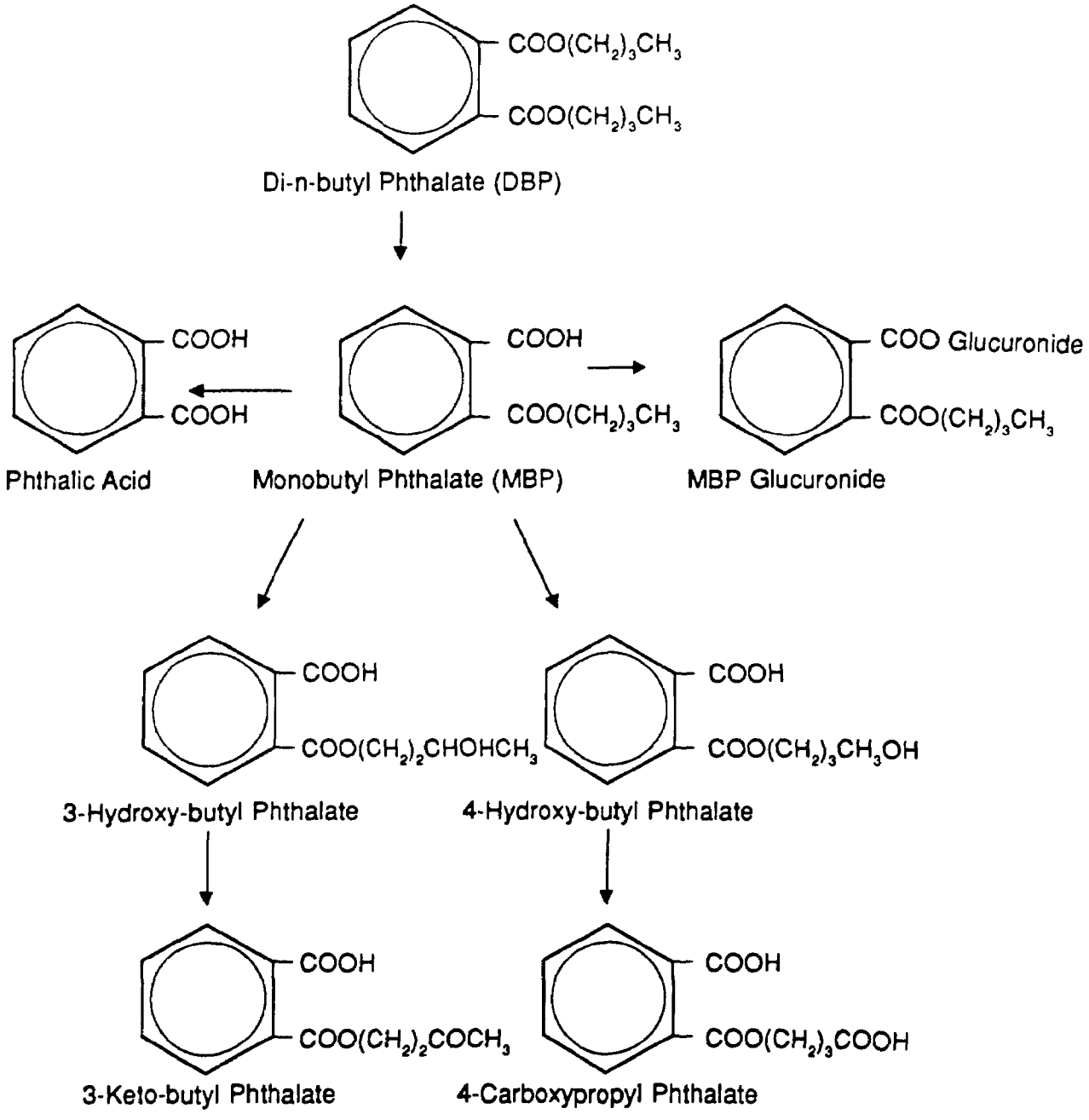


FIGURE 2-3. Metabolic Scheme for Di-n-butyl Phthalate in Animals

Source: Adapted from Albro and Moore 1974; Foster et al. 1982; Tanaka et al. 1978.

which only 3.5% was excreted unconjugated. The authors indicated that this difference might explain why exposure to di-n-butyl phthalate causes greater testicular damage in rats than in hamsters (see Section 2.2.2.6.)

2.3.3.3 Dermal Exposure

No studies were located regarding metabolism in humans and animals following dermal exposure to di-n-butyl phthalate.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding excretion in humans or animals following inhalation exposure to di-n-butyl phthalate.

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans following oral exposure to di-n-butyl phthalate.

Studies in laboratory animals (rats, hamsters and guinea pigs) indicate that 63 to 97% of an oral dose of di-n-butyl phthalate is eliminated in the urine within 24 hours, with 85 to 100% recovered by 48 hours (Foster et al. 1982; Tanaka et al. 1978; Williams and Blanchfield 1975). The fraction of the dose that was not accounted for in the urine was present in the feces. Excretion was essentially complete by 48 hours after administration of a single oral dose (Tanaka et al. 1978).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans following dermal exposure to di-n-butyl phthalate.

In rats, following a single dermal application of ^{14}C-labeled di-n-butyl phthalate, 10-12% of the administered dose was excreted in urine and 1% was excreted in the feces (Elsisi et al. 1989). Seven days after application, 60% of the applied dose had been excreted.

2.4 RELEVANCE TO PUBLIC HEALTH

Toxic effects caused by di-n-butyl phthalate exposure have not been well characterized in humans. Based on the findings in animal studies, toxic effects in humans would not be expected at typical exposure levels, since effects in animals were seen only at very high doses (1-2% di-n-butyl phthalate in the diet in oral studies).

2. HEALTH EFFECTS

In animals, the main target for di-n-butyl phthalate is the reproductive system. In males, atrophy of the seminiferous tubules and decreased sperm counts have been observed in several species, with the more sensitive species being those with less ability to conjugate the primary metabolite of di-n-butyl phthalate. The testicular effects observed were dose-related and were, at least in part, reversible. Developmental effects have also been observed. Di-n-butyl phthalate has been demonstrated to be fetotoxic in rats and mice, and limited data indicate that di-n-butyl phthalate may also be teratogenic.

Death. In laboratory animals, the oral LD_{50} from a single dose was estimated to be between 20,000 and 25,000 mg/kg for the rat, with some deaths occurring at 10,000 mg/kg (White et al. 1983). An LD_{10} of 2,500 mg/kg was identified in mice (Hardin et al. 1987). None of the acute studies provided details about cause of death. No human deaths have been reported as a result of exposure to di-n-butyl phthalate. Considering the high LD_{50} values for animals, it is unlikely that a human would accidentally ingest an amount of di-n-butyl phthalate that would be fatal.

Systemic Effects. A number of studies in animals indicate that di-n-butyl phthalate may interfere with energy metabolism in liver mitochondria, both in vivo (Murakami et al. 1986a, 1986b), and in vitro (Inouye et al. 1978; Melnick and Schiller 1985). Exposure in vivo was accompanied by an increased number of mitochondria in liver cells, suggesting a compensation for the inhibiting effects of di-n-butyl phthalate (Murakami et al. 1986a). Zonal and focal necrosis of liver cells was also observed in one study (Murakami et al. 1986a). This could be related to the inhibition of mitochondrial activity, since when the energy needs of cells cannot be met, the cells die. No di-n-butyl phthalate associated liver injury has been reported in humans.

Several animal studies indicate that the kidney is not significantly affected by di-n-butyl phthalate (Kawano 1980a; Nikonorow et al. 1973; Oishi and Hiraga 1980a). Slight changes in kidney weight have been associated with oral exposure to di-n-butyl phthalate in rats or mice (BIBRA 1986; Oishi and Hiraga 1980a), but in the absence of other data, this does not constitute evidence of injury.

Exposure to di-n-butyl phthalate can decrease body weight in animals (BIBRA 1986; Gray et al. 1982; Kawano 1980a; Nikonorow et al. 1973), but this is generally not considered a sensitive or specific indicator of toxicity.

Immunological Effects. In human dermal sensitization studies, cosmetic preparations containing di-n-butyl phthalate did not cause skin sensitization. Negative results were also noted in rabbits (Cosmetic Ingredient Review Committee 1985; Lehman 1955).

Neurological Effects. Limited evidence suggests that exposure of humans to high levels of di-n-butyl phthalate may cause neurological symptoms such as dizziness, pain, and numbness (Milkov et al. 1973). Increased brain weight was found in rats following 6 months of inhalation exposure to di-n-butyl phthalate (Kawano 1980a), but the clinical relevance of this observation is not clear. Available studies in animals do not suggest that the nervous system is a target organ following oral exposure to di-n-butyl phthalate, but this has not been formally investigated.

Developmental Effects. No developmental effects of di-n-butyl phthalate have been reported in humans. In animals, di-n-butyl phthalate has been demonstrated to be toxic to fetuses (Hardin et al. 1987; Killinger et al. 1988a,b; Nikonorow et al. 1973; Shiota et al. 1980; Shiota and Nishimura 1982). In some, but not all, cases, fetal toxicity may have been related to maternal toxicity. Di-n-butyl phthalate given to females during pregnancy resulted in an increased number of resorptions and a decreased number of viable litters. In one study in mice, di-n-butyl phthalate was reported to cause teratogenic effects (Shiota and Nishimura 1982), but teratogenicity has not been observed in other developmental studies. Since the data are limited and inconsistent, it is not possible to judge conclusively whether di-n-butyl phthalate is a teratogen or not.

Reproductive Effects. High oral doses of di-n-butyl phthalate at acute and intermediate exposure durations affect male reproductive systems of rats and guinea pigs. Effects include decreased testes weight, decreased number of spermatocytes and degeneration of the seminiferous tubules of the testes (BIBRA 1986; Cater et al. 1977; Gray et al. 1982; Murakami et al. 1981a, 1986b; Oishi and Hiraga 1980b; Tanino et al. 1987). Limited data suggest that exposure to di-n-butyl phthalate may be associated with decreased sperm density in humans as well (Murature et al. 1987), but this is not certain. Three weeks after discontinuation of di-n-butyl phthalate administration to rats, regeneration of seminiferous tubules and active spermatogenesis were observed, suggesting these effects may be reversible (Tanino et al. 1987). In contrast to rats and guinea pigs, mice and Syrian hamsters are relatively resistant to the testicular effects of di-n-butyl phthalate (Gray et al. 1982). The basis of this species variation is not known, but could be related to species differences in the ability to

conjugate the primary metabolite of di-n-butyl phthalate (Foster et al. 1982). Since no information was located concerning human metabolism of di-n-butyl phthalate, the relevance of these observations to public health is unknown.

Di-n-butyl phthalate also has adverse effects on reproduction in females. Mice fed 1,300 mg/kg/day in the diet for 4 months before and during breeding had fewer live pups per litter and a lower proportion of pups born alive (Lamb et al. 1987; Reel et al. 1987). Similarly, exposure of rats or mice to doses of about 1,000 mg/kg/day of di-n-butyl phthalate in the diet during gestation resulted in marked increases in fetal and neonatal mortality (Killinger et al. 1988a, 1988b). These effects did not appear to be a result of maternal toxicity, indicating that the fetus is more sensitive to di-n-butyl phthalate than the dam. Still, it should be noted that significant fetotoxicity occurred only at very high dose rates, and it does not seem likely that this effect is of concern to humans exposed to the low levels of di-n-butyl phthalate typically encountered in air, food or water.

Genotoxic Effects. Available in vitro genotoxicity data are summarized in Table 2-4. Di-n-butyl phthalate has tested negative or marginally positive in gene mutation and chromosomal aberration studies. These results suggest that di-n-butyl phthalate may be weakly mutagenic in vitro. The significance of these findings to the intact mammalian organism is not known because in vivo genotoxicity studies have not been conducted.

Cancer. The carcinogenic potential of di-n-butyl phthalate has not been thoroughly studied. An early investigation did not detect any carcinogenic effects in rats exposed for 15 to 21 months to doses of 100 to 500 mg/kg/day in the diet (Krauskopf 1973), but the data were too limited and the doses were too low to draw a firm conclusion.

Carcinogenicity studies on other phthalate esters have been mostly negative or equivocal, although there is sufficient evidence in animals to conclude that di-ethyl hexyl phthalate (DEHP) causes hepatocellular carcinomas in rats and mice (EPA 1987). The significance of this observation to cancer risk of di-n-butyl phthalate is uncertain. Consequently, it is not possible to evaluate the carcinogenic risk of di-n-butyl phthalate to humans without more investigation.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

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

TABLE 2-4. Genotoxicity of Di-n-butyl Phthalate *In Vitro*

End Point	Species (Test System)	Results: With Activation	Results: Without Activation	Reference
Prokaryotic organisms:				
Gene mutation	*Salmonella typhimurium*	-	-	Florin et al. 1980; Rubin et al. 1979; Zeiger et al. 1985
	S. typhimurium	-	(+)	Seed 1982
	S. typhimurium	-	+	Agarwal et al. 1985
Eukaryotic organisms:				
Fungi:				
Gene mutation	*Saccharomyces cerevisiae*	-	-	Shahin and Borstel 1977
Mammalian cells:				
Gene mutation	Mouse lymphoma	+	-	Hazleton Biotechnologies 1986
Chromosomal aberrations	Chinese hamster ovary cells	No data	(+)	Ishidati and Odashima 1977
Cell transformation	Balb 3T3	No data	-	Litton Bionetics 1985a

- = negative result; (+) = marginally positive; + = positive result.

2. HEALTH EFFECTS

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 or cell 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 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 (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc and selenium). Biomarkers of exposure to di-n-butyl phthalate are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by di-n-butyl phthalate are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Di-n-butyl Phthalate

The presence of di-n-butyl phthalate has been reported in a number of human tissues and fluids. Di-n-butyl phthalate has been found in adipose tissue obtained from surgical procedures or autopsies (Mes et al. 1974; Stanley 1986), in lipid-rich atherosclerotic plaques

(Ferrario et al. 1985), in seminal fluid (Murature et al. 1987), and in blood serum (Ching et al. 1981a; Stanley 1986). No study identified the source, amount, or duration of exposure to di-n-butyl phthalate associated with levels in the body. A study comparing surgical patients having known plasticizer exposure from intravenous bags and tubing with controls without known exposure found no correlation between exposure and serum levels of di-n-butyl phthalate (Ching et al. 1981a). There was no quantitative relationship between the concentration of di-n-butyl phthalate in seminal fluid and sperm count (Murature et al. 1987). Thus, measurements of di-n-butyl phthalate in body tissues and fluids can indicate that exposure has taken place, but not the amount or duration of exposure.

2.5.2 Biomarkers Used to Characterize Effects Caused by Di-n-butyl Phthalate

Effects caused by di-n-butyl phthalate exposure in animals include liver changes and effects on development and reproduction. None of these effects appear to be specific to di-n-butyl phthalate exposure. Liver changes, such as altered enzymatic activity and peroxisome proliferation, are induced by many other chemicals (Popp et al. 1989). Testicular effects may be due to interference with zinc metabolism, which can also be caused by exposure to cadmium, manganese, and other substances (Foster et al. 1980). These and other effects associated with di-n-butyl phthalate exposure do not appear to be sufficiently specific to serve as biomarkers of effects.

2.6 INTERACTION WITH OTHER CHEMICALS

Administration of zinc provides some protection against the testicular toxicity of di-n-phthalate exposure in rats (Cater et al. 1977). No other studies were located regarding the interaction of di-n-butyl phthalate with other chemicals. Schulsinger and Mullgaard (1980) reported that humans exposed to a mixture of three phthalate esters, including di-n-butyl phthalate, did not develop dermal sensitization, but since di-n-butyl phthalate is negative for skin sensitization, these results shed little light on possible interactions.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

There are no data in humans to suggest that any segment of the human population is unusually susceptible to the effects of di-n-butyl phthalate. However, in studies in animals, fetal death was reported at dietary levels at which the mothers survived. This suggests that the fetus may be somewhat more susceptible to di-n-butyl phthalate than the adult, and that it may be prudent to consider pregnant females more susceptible to di-n-butyl phthalate than other adults.

2.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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-butyl phthalate is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of di-n-butyl phthalate.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.8.1 Existing Information on Health Effects of Di-n-butyl Phthalate

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to di-n-butyl phthalate are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of di-n-butyl phthalate. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information. Limited data are available on effects in humans, consisting of an occupational study of workers exposed to mixtures of plasticizers and dermal sensitization studies conducted to evaluate the effects of di-n-butyl phthalate in cosmetic products. Data from animal studies are more extensive. As a result of early findings on testicular effects of di-n-butyl phthalate, most studies have tended to concentrate mainly on developmental and reproductive effects. A few studies provide data on systemic effects, but since these appear to be minor, research in this area has not been extensive. No data are available on the chronic effects of di-n-butyl phthalate, or on its carcinogenic potential.

2.8.2 Identification of Data Needs

Acute-Duration Exposure. The male reproductive system appears to be the most sensitive target organ for acute-duration oral exposure to di-n-butyl phthalate in animals. However, acute-duration experiments on developmental toxicity of di-n-butyl phthalate did not establish a

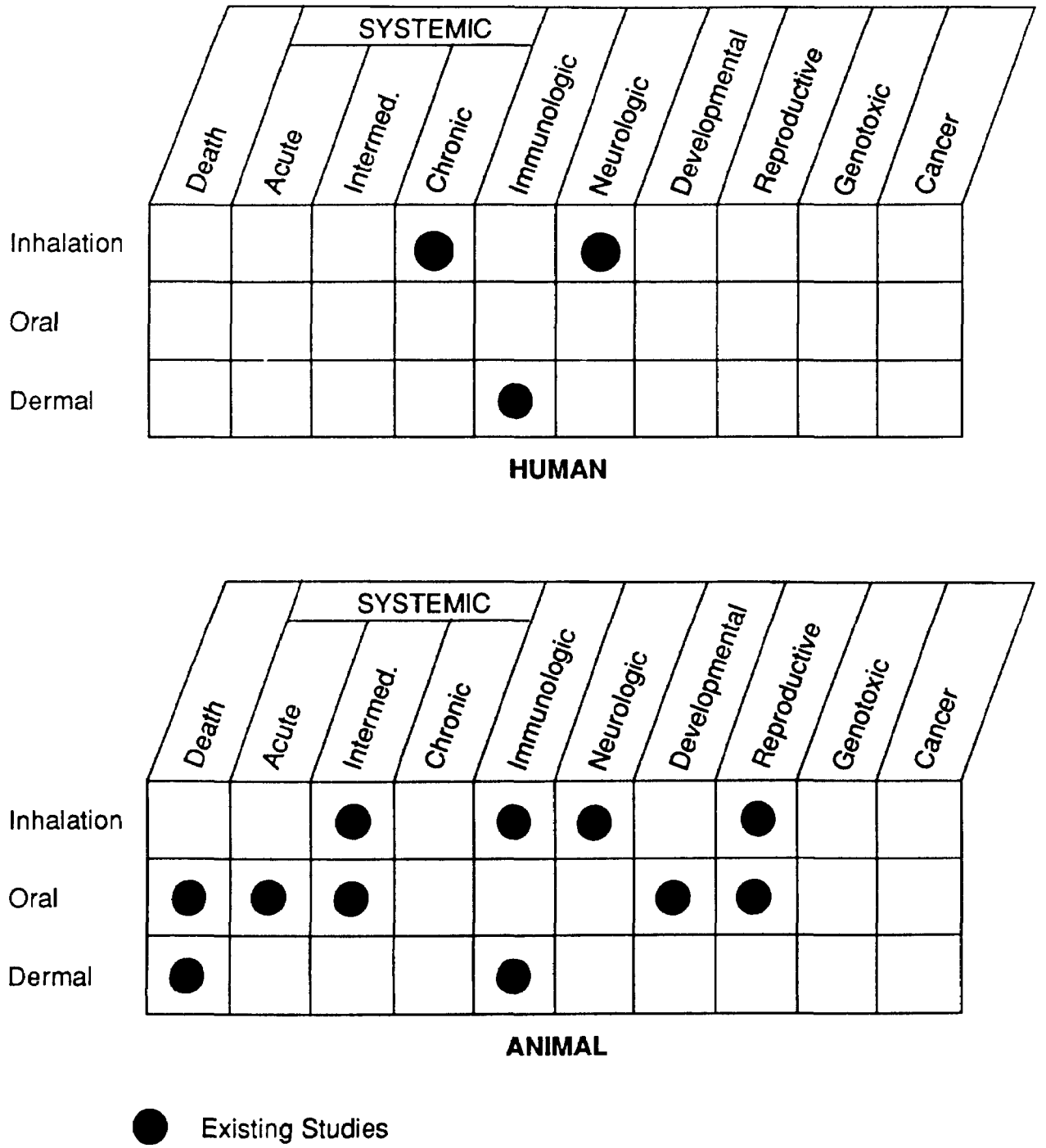


FIGURE 2- 4. Existing Information on Health Effects of Di-n-Butyl Phthalate

threshold (Hardin 1987) so it is possible that developmental rather than reproductive toxicity may be the critical effect for acute-duration exposure. A LOAEL of 1,000 mg/kg/day was established for decreased testis weight in rats following 7 days of gavage exposure (Oishi and Hiraga 1980a); however, only one dose level was used in this study and so the threshold for the effect is not reliably identified and no acute oral MRL could be derived. The mechanism of testicular damage by di-n-butyl phthalate may involve interference with zinc metabolism (Foster et al. 1980), and further investigations to establish the mechanism would assist in assessing the relevance of animal toxicity to human risk. No information was located on effects in humans of acute-duration oral exposure. Systemic effects caused by acute-duration oral exposure in animals are generally mild, and include changes in liver and kidney weight and changes in biochemical parameters. No information was located concerning target organs following acute-duration inhalation or dermal exposure to di-n-butyl phthalate in animals or humans, and no acute inhalation MRL could be derived. Additional information concerning the target organs and mechanism of toxicity of di-n-butyl phthalate exposure by the inhalation, oral, and dermal routes would be useful to assess the risks to populations surrounding hazardous waste sites that might be exposed to di-n-butyl phthalate for brief periods.

Intermediate-Duration Exposure. For intermediate-duration oral exposure to di-n-butyl phthalate, the developing fetus and the female reproductive system appear to be the most sensitive target systems. An intermediate oral MRL was derived based on decreased body weights of offspring of female rats exposed during pregnancy and lactation for 48 days at doses of 125 mg/kg/day or more in the diet (Killinger et al. 1988a). No information was located concerning the mechanism of developmental toxicity, and such data would be useful to assist in extrapolating the human developmental or reproductive toxicity of di-n-butyl phthalate exposure. Systemic effects caused by intermediate-duration oral exposure in animals are primarily effects on the liver (changes in enzyme activity, peroxisome proliferation), and inhalation exposure causes changes in organ weights. Studies of toxicity using the inhalation and dermal routes of exposure would be valuable in establishing the levels causing developmental or reproductive toxicity in animals by these routes. Additional information concerning the target organs and mechanism of toxicity of di-n-butyl phthalate exposure by the inhalation, oral, and dermal routes would be useful to assess the risks to populations surrounding hazardous waste sites that might be exposed to di-n-butyl phthalate for intermediate durations.

Chronic-Duration Exposure and Cancer. No information was located concerning the toxic effects of chronic-duration exposure to di-n-butyl phthalate in humans or animals by any route of exposure. Studies to establish the target organs and levels causing effects following

chronic-duration exposure to di-n-butyl phthalate by inhalation, oral and dermal exposure would be useful to assess the risks to populations surrounding hazardous waste sites that might be exposed to di-n-butyl phthalate for long periods of time.

No information was located indicating that di-n-butyl phthalate is carcinogenic to humans or animals. A study of carcinogenicity of dietary exposure in rats and mice is planned (Section 2.8.3). When results of this study become available, they may suggest areas where additional information would be useful for evaluating carcinogenic potential, such as route dependence, mechanism of action, and species specificity.

Genotoxicity. A limited number of *in vitro* tests for genotoxicity suggest that di-n-butyl phthalate may have weak genotoxic potential. No *in vivo* studies have been conducted. *In vivo* genotoxicity studies would be valuable in determining whether di-n-butyl phthalate has mutagenic potential and, if so, what the possible mechanism of genotoxicity might be.

Reproductive Toxicity. Oral exposure to di-n-butyl phthalate causes testicular damage in male animals. Species differences are apparent, with rats being more sensitive than mice. Limited information suggests that testicular damage may not occur following inhalation exposure in rats. Reproduction studies in rats and mice have shown that oral di-n-butyl phthalate exposure has toxic effects on female reproductive ability. No information is available on the effects of di-n-butyl phthalate exposure on human reproduction, or on the effects following dermal exposure in animals. A study of reproductive toxicity of dietary exposure in rats is planned (Section 2.8.3). After this study is completed, it will be possible to identify additional work where information would be useful to provide better understanding of the mechanism of action of di-n-butyl phthalate on male and female reproduction, route dependence, multi-generation effects, and species differences. Such information would be useful to assess the significance of the animal results to human reproductive risk.

Developmental Toxicity. Studies in rats and mice have shown that oral di-n-butyl phthalate exposure of pregnant females is toxic to fetuses, and one study in mice suggested that high levels of exposure to di-n-butyl phthalate may be teratogenic. No data were located concerning developmental effects in humans or by routes other than oral in animals. A study of developmental toxicity of dietary exposure in rats is planned (Section 2.8.3). Evaluation of the results of this study may indicate areas where additional information concerning

mechanism of developmental toxicity, species specificity, and route dependence would be valuable to characterize the potential for di-n-butyl phthalate exposure to cause developmental toxicity in humans.

Immunotoxicity. There are a number of studies in humans and animals which indicate that di-n-butyl phthalate is not a skin sensitizing agent following dermal exposure. Inhalation exposure does not appear to cause immunologic effects, but only limited end points have been investigated. No studies were located using oral exposure or assessing the effects of di-n-butyl phthalate on other aspects of the immune system. Tests of several additional endpoints of humoral and cell-mediated immune function would be valuable in assessing the sensitivity of this system to di-n-butyl phthalate.

Neurotoxicity. Limited data in humans suggest that high level inhalation exposure to di-n-butyl phthalate may have the potential to cause neurological damage. Additional studies designed to test for neurological effects in animals would be useful to assess the levels of di-n-butyl phthalate capable of causing neurotoxicity.

Epidemiological and Human Dosimetry Studies. Very limited epidemiological studies have been performed, and generally involved exposure to a mixture of plasticizers at poorly-characterized levels. Studies of people occupationally exposed to di-n-butyl phthalate would be valuable in assessing the effects of di-n-butyl phthalate on human health. Since the most significant effects in animals are on spermatogenesis and reproduction, epidemiology studies of reproductive parameters in humans exposed to di-n-butyl phthalate would be particularly relevant. Such studies would be most valuable if dosimetry methods could be developed to provide reliable exposure data to accompany health effects data. This would assist in establishing cause/effect relationships and developing methods to monitor individuals living near hazardous waste sites.

Biomarkers of Exposure and Effect. The presence and concentration of di-n-butyl phthalate can be measured in a variety of biological tissues and fluids, but no information was located which would allow correlation of body levels with source, route, amount, or duration of exposure to di-n-butyl phthalate. The primary metabolite of di-n-butyl phthalate in several species is monobutyl phthalate, and so monobutyl phthalate or its glucuronide conjugate could possibly serve as a specific biomarker of exposure to di-n-butyl phthalate. Additional studies to determine the relationship between body levels of di-n-butyl phthalate and monobutyl phthalate and exposure would be valuable to develop methods for identifying and monitoring populations with high exposure to di-n-butyl phthalate.

No known biomarkers of effect of di-n-butyl phthalate were identified. Studies to identify some early indication of impending injury to the male and female reproductive systems, perhaps based on the interference of zinc metabolism, would be valuable in assessing likely health consequences in people with above-average exposure to di-n-butyl phthalate.

Absorption, Distribution, Metabolism, and Excretion. Studies in laboratory animals indicate that di-n-butyl phthalate given orally is readily absorbed, mainly as the metabolite monobutyl phthalate, and subsequently is rapidly excreted. Limited data exist regarding inhalation and dermal absorption. Studies on the absorption and metabolism of di-n-butyl phthalate by the inhalation and dermal routes would be valuable in evaluating human health risk by these routes of exposure.

Comparative Toxicokinetics. Syrian hamsters appear to be relatively resistant to the testicular effects of di-n-butyl phthalate compared to the rat. A comparative metabolic study with rats and hamsters indicated some quantitative differences between the two species with respect to the excretion of metabolites in the urine. Additional comparative studies, perhaps with other species, may add to our understanding of the mechanisms of toxicity to the male reproductive organs. Since it is well known that there are a wide variety of esterases with varying affinity for different substrates, further information on the substrate specificities of the esterases in various species could help to understand the biological mechanisms behind the species differences in response to di-n-butyl phthalate.

2.8.3 On-going Studies

Information located concerning on-going studies with di-n-butyl phthalate is summarized in Table 2-5. These include studies to evaluate the mutagenic and carcinogenic potential of di-n-butyl phthalate, as well as effects on reproduction and development.

TABLE 2-5. On-going Studies on Di-n-butyl Phthalate

Investigator	Affiliation	Research Description	Sponsor
A.C. Peters	Batelle Memorial Institute	Prechronic dietary study in mice and rats	NIEHS
-	Batelle Memorial Institute	Carcinogenicity study in rats and mice (planned)	NIEHS
-		Reproductive/ developmental toxicity in rats	ATSDR/NTP

NIEHS = National Institute of Environmental Health Sciences; ATSDR = Agency for Toxic Substances and Disease Registry; NTP = National Toxicology Program.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

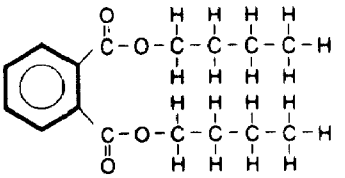
Table 3-1 lists common synonyms, trade names and other pertinent identification information for di-n-butyl phthalate.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Table 3-2 lists important physical and chemical properties of di-n-butyl phthalate.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of Di-n-butyl Phthalate

	Value	Reference
Chemical name	Di-n-butyl phthalate	NLM 1988
Synonyms	Butylphthalate; dibutylphthalate; DBP; 1,2-benzene-dicarboxylic acid, dibutyl ester	NLM 1988
Trade names	Caswell No. 292; Celluflex DBP; Polycizer DBP; Staflex DBP; Uniflex DBP	NLM 1988
Chemical formula	$C_{16}H_{22}O_4$	NLM 1988
Chemical structure		
Identification numbers:		
CAS Registry	84-74-2	NLM 1988
NIOSH RTECS	TI0875000	HSDB 1988
EPA Hazardous Waste	U069	NLM 1988
OHM/TADS	7216617	HSDB 1988
DOT/UN/NA/IMCO Shipping	NA9095	NLM 1988
HSDB	922	NLM 1988
NCI	No data	

CAS = Chemical Abstracts Service; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute.

TABLE 3-2. Physical and Chemical Properties of Di-n-butyl Phthalate

Property	Value	Reference
Molecular weight	278.35	Weast 1985
Color	Colorless to faint yellow	Verschueren 1983 HSDB 1988
Physical state	Oily liquid	Verschueren 1983
Melting point	-35°C	Verschueren 1983
Boiling point	340°C	Weast 1985
Density at 20°C	1.047	Weast 1985
Odor	Odorless to slight ester odor	Sax and Lewis 1987; HSDB 1988
Odor threshold:		
Water	Odorless	
Air	Odorless	
Solubility:		
Water at 20°C	8.7-13 mg/L	DeFoe et al. 1990
Organic solvents	Soluble in alcohol, ether, benzene	Weast 1985
Partition coefficients:		
Log octanol/water	4.72-5.60	Mabey et al. 1982; Howard 1989
Log K_{oc}	5.23	Mabey et al. 1982
Vapor Pressure at 25°C	$1.0x10^{-5}$-$1.4x10^{-5}$ mmHg	Mabey et al. 1982; Howard 1989
Henry's law constant	$2.8x10^{-7}$-$4.6x10^{-7}$ atm-m^3/mol	Mabey et al. 1982; Howard 1989
Autoignition temperature	398.8°C	Sax and Lewis 1987
Flashpoint	171°C	Sax and Lewis 1987
	157.22°C	ACGIH 1986
Flammability limits	lower: 0.5% at 235°C	HSDB 1988
Conversion factors	1 ppm = 11.4 mg/m^3 1 mg/m^3 = 0.088 ppm	

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Di-n-butyl phthalate is produced commercially by the esterification of phthalic anhydride with n-butyl alcohol in the presence of concentrated sulfuric acid as a catalyst. Excess alcohol is recovered and recycled and the di-n-butyl phthalate is purified by vacuum distillation and/or activated charcoal (HSDB 1988; Perwak et al. 1981).

Production volumes published for di-n-butyl phthalate usually also include the production volumes for diisobutyl phthalate. The available data indicate that production of these compounds peaked at 17,200 kkg in 1973, dipped sharply to 5,600 kkg in 1975, and then increased gradually to 11,400 kkg in 1987 (Perwak et al. 1981; USITC 1988).

Currently there are eight producers of di-n-butyl phthalate in the United States: Aristech Chemical Corp., Neville Island, Pennsylvania; BASF Corp., Kearny, New Jersey; Mobay Corp., Carteret, New Jersey; Eastman Kodak Co., Kingsport, Tennessee; Hatco Corp., Fords, New Jersey; Nuodex, Inc., Chestertown, Maryland; Union Camp Corp., Dover, Ohio; and Unitex Chemical Co., Greensboro, North Carolina (SRI 1988; USITC 1988).

4.2 IMPORT

Imports of di-n-butyl phthalate were 747 kkg in 1977 and 303 kkg in 1981. No quantitative data were located on exports of di-n-butyl phthalate. However, total phthalate ester exports in 1977 were 42,500 kkg and di-n-butyl phthalate is estimated to be about 1% of total phthalate production. On that basis, about 425 kkg of di-n-butyl phthalate were probably exported in 1977 (HSDB 1988; Perwak et al. 1981).

4.3 USE

Di-n-butyl phthalate is used primarily as a specialty plasticizer for nitrocellulose polyvinyl acetate and polyvinyl chloride. It has been used in plastisol formulations for carpet back coating and other vinyl compounds. Di-n-butyl phthalate has also been used as an adjusting agent for lead chromate pigments, as a concrete additive, as an insect repellant for the impregnation of clothing, as a solvent for perfume oils, and as a stabilizer in rocket propellants (Perwak et al. 1981; Sax and Lewis 1987; Windholz 1983). In 1977, about 45% of di-n-butyl phthalate was used for polyvinyl chloride plasticizers, 50% for other polymers, and 5% for nonplasticizer uses (Perwak et al. 1981). Current usage information was not located.

4.4 DISPOSAL

Since di-n-butyl phthalate is listed as a hazardous substance, disposal of wastes containing di-n-butyl phthalate is controlled by a number of federal regulations (see Chapter 7). Land disposal restrictions (treatment/standards) currently apply to di-n-butyl phthalate wastes. Di-n-butyl phthalate wastes may be incinerated by the rotary kiln method or other suitable treatment methods (EPA 1988a, 1989b).

It is estimated that wastes containing 6,300 kkg of di-n-butyl phthalate were disposed in landfills and 200 kkg of di-n-butyl phthalate were incinerated in 1977. In addition, 300 kkg of di-n-butyl phthalate were released to air and 300 kkg to water during production, transportation, etc. (Perwak et al. 1981).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Di-n-butyl phthalate is one of the phthalate esters which has been widely used in making flexible plastics that are found in many common consumer products, including home furnishings, paints, clothing, and cosmetic products. Because of its many uses, di-n-butyl phthalate is widespread in the environment and has been identified at low levels in air, water, and soil. Therefore, humans may be exposed to di-n-butyl phthalate both by inhalation and ingestion of water or food containing di-n-butyl phthalate. Di-n-butyl phthalate has been identified in 47 of 1,177 NPL sites. The frequency of these sites within the United States can be seen in Figure 5-1.

In air, di-n-butyl phthalate may be adsorbed to particulate matter or occur as a vapor. Di-n-butyl phthalate is expected to decompose in the air, or be transferred to water and soil by wet (snow or rain) or dry (wind and settling) deposition. Di-n-butyl phthalate is taken up from water by a variety of aquatic organisms. In water and soil, di-n-butyl phthalate is subject to microbial degradation. Both aerobic and anaerobic degradation of di-n-butyl phthalate have been reported. Exposure of the general population to di-n-butyl phthalate may occur through contact with contaminated air, water, or food.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Although di-n-butyl phthalate has low volatility, its widespread use in many thin polymeric sheets and coatings provides large surface areas for volatilization during the manufacture, use and disposal of these products. In addition, disposal at dump sites and disintegration of the plastics allow for dispersal of small particulates into the air. It is estimated that 300 kkg of di-n-butyl phthalate were released to air from these sources in 1977 (Perwak et al. 1981).

5.2.2 Water

Di-n-butyl phthalate may be released into surface waters from industrial sources (Sheldon and Hites 1979). An estimated 300 kkg of di-n-butyl phthalate were released to water in 1977 (Perwak et al. 1981).

Di-n-butyl phthalate has also been detected in 5% of the urban runoff samples from 2 of the 19 cities tested by EPA (Howard 1989). Concentrations in this urban wastewater ranged from 0.5 to 11 µg/L. Sewage sludge has been shown to concentrate di-n-butyl phthalate about

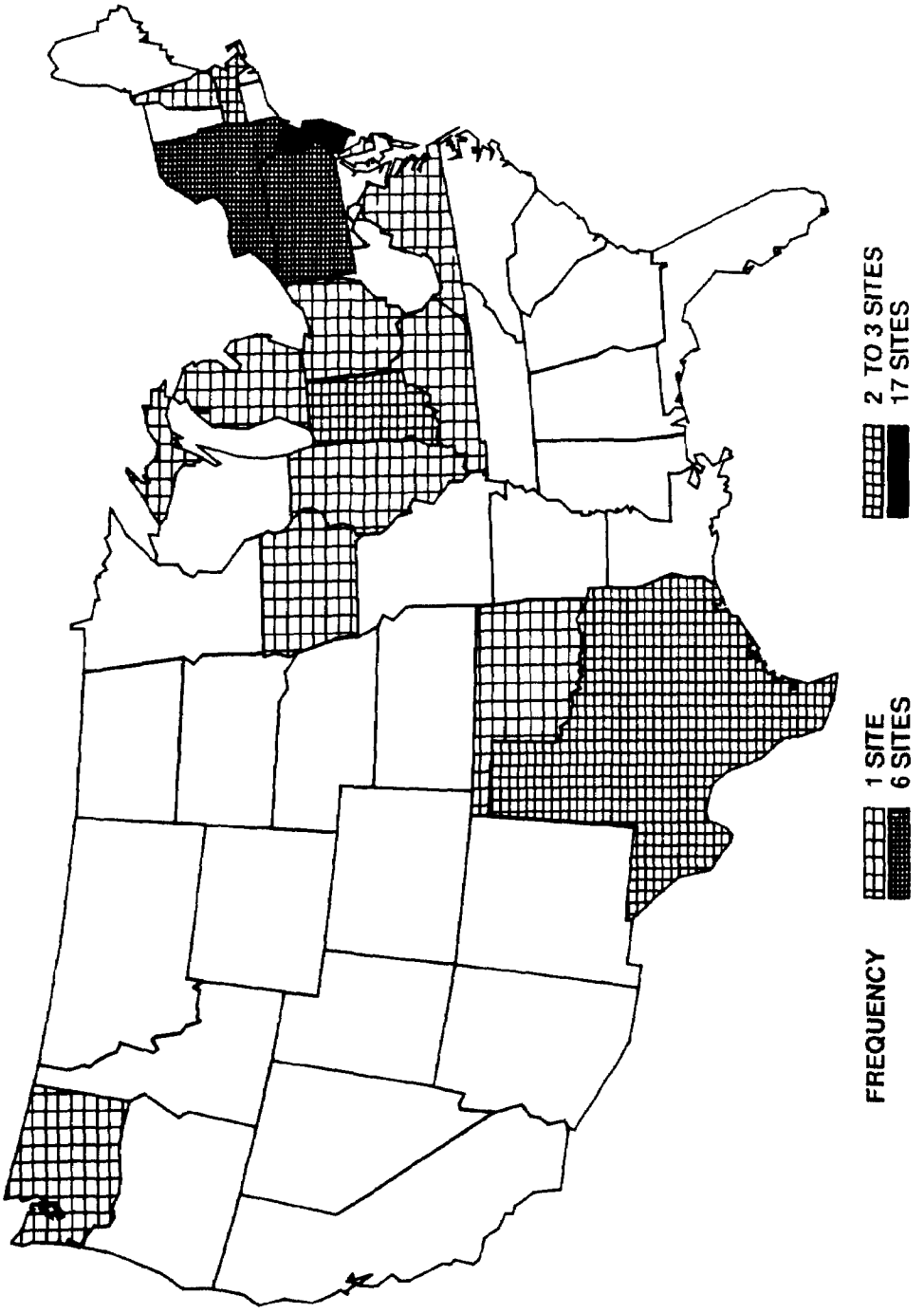


FIGURE 5-1. Frequency of Sites with Di-n-butyl Phthalate Contamination

25-fold relative to the starting material. A concentration of 966 μg/L sludge was reported by Feiler et al. (1980). Disposal of secondary sewage effluent by rapid infiltration into the subsurface has been reported to produce a plume of contaminated groundwater over 3,500 meters long (Barber et al. 1988).

5.2.3 Soil

No specific release of di-n-butyl phthalate to soils has been reported. Most data on the release of di-n-butyl phthalate to soil relate to presence of di-n-butyl phthalate in lake, river and ocean sediments. Di-n-butyl phthalate has been identified in river and ocean sediments at points of sewage outflow from urban areas (Fallon and Horvath 1985; Swartz et al. 1983). Also, di-n-butyl phthalate may seep into soil from di-n-butyl phthalate containing sewage sludge that is deposited on land.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Although di-n-butyl phthalate has low volatility, it has been reported as particulate in the atmosphere and as a vapor. In the air, di-n-butyl phthalate is transported from its origin and is subject to both wet (rain and snow) and dry (wind and settling) deposition on the earth's surfaces (Atlas and Giam 1981). Eisenreich et al. (1981) calculated that wet and dry deposition of di-n-butyl phthalate into the five Great Lakes amounted to 48 kkg per year.

Although di-n-butyl phthalate is only poorly soluble in water, it may be transported in water following formation of chemical complexes between di-n-butyl phthalate and humic substances (Callahan et al. 1979). The adsorption of di-n-butyl phthalate onto particulate matter is greater in salt water than in fresh water (Al-Omnan and Preston 1987). Adsorption onto soil and sediments appear to be a significant sink for di-n-butyl phthalate. It has been demonstrated that di-n-butyl phthalate is rapidly adsorbed from seawater onto marine sediment (Sullivan et al. 1982).

In hazardous waste sites, the presence of common organic solvents such as alcohols and ketones may increase the solubility of relatively water insoluble compounds such as di-n-butyl phthalate, thus increasing the amounts that may leach from the site into the subsoil and into groundwater. For example, 1-octanol-saturated water increases the solubility of di-n-butyl phthalate approximately 6 times its normal water solubility (Nyssen et al. 1987).

5. POTENTIAL FOR HUMAN EXPOSURE

Data indicate that di-n-butyl phthalate can be taken up by a variety of organisms. Studies using radioactively-labeled di-n-butyl phthalate have shown a substantial accumulation of radioactivity in aquatic invertebrates (Sanders et al. 1973) and fish (Wofford et al. 1980). Most of the accumulated radioactivity is apparently in the form of the primary metabolite, monobutyl phthalate (Howard 1989). In greenhouse studies, Shea et al. (1982) demonstrated dose-dependent uptake of di-n-butyl phthalate from soils into corn, soybean and wheat seedlings.

5.3.2 Transformation and Degradation

5.3.2.1 Air

In air, di-n-butyl phthalate in vapor form would be expected to react with hydroxyl radicals with a half-life of about 18 hours (EPA 1987c), but this has not been studied. For di-n-butyl phthalate adsorbed to airborne particles, the half-life may be considerably longer, but this also has not been studied.

5.3.2.2 Water

In water, di-n-butyl phthalate may be degraded by several pathways. A modeling system presented by Wolfe et al. (1980a) predicted that at steady state nearly all of the di-n-butyl phthalate in a flowing stream would remain in transit. In a pond, 3% could be expected to be lost by hydrolysis, 1% by photolysis, 6% by volatilization, and 32% by biodegradation. Under actual environmental conditions, the rate of biodegradation in ponds and lakes will depend on conditions (e.g., the level of degradative organisms present), and could be higher or lower than this calculated value.

A relatively large number of water microorganisms appear to be capable of biodegrading di-n-butyl phthalate. In Mississippi River water, 172 microorganisms per mL of water were found that could utilize di-n-butyl phthalate. In the delta area there were 55 microorganisms per mL of water that were capable of degrading di-n-butyl phthalate. Biodegradation studies of di-n-butyl phthalate in water from 6 sites in Louisiana, Mississippi and Florida showed that the time to nondetection was 2 to 27 days (Walker 1984).

In laboratory experiments, the time sequence for degradation of di-n-butyl phthalate indicated microorganism adaptation (Cripe et al. 1987). An initial lag phase of 1 to 2 days was followed by rapid loss of the parent compound. Respiking the water sample with di-n-butyl phthalate resulted in the rapid disappearance of di-n-butyl phthalate without a lag period, indicative of the presence of a large induced microbial population with the ability to degrade di-n-butyl phthalate.

5. POTENTIAL FOR HUMAN EXPOSURE

Activated sludge wastewater treatment systems remove about 90% of the di-n-butyl phthalate from the sewage influent. The biodegradation products have not been identified and may depend on the residence time in the reaction system (Kurane et al. 1979; O'Grady et al. 1985; Petrasek et al. 1983). Under anaerobic conditions, activated sludge completely degraded di-n-butyl phthalate to carbon dioxide and methane over a period of 20 days (Hannah et al. 1986).

5.3.2.3 Soil

Microorganisms in soil and sediments appear to be capable of degrading di-n-butyl phthalate rapidly (Inman et al. 1984; Johnson et al. 1984; Taylor et al. 1981; Walker et al. 1984). In fortified river sediment samples, di-n-butyl phthalate was degraded in 2 to 13 days (Walker 1984), and lake sediment samples degraded di-n-butyl phthalate in 28 days (Johnson et al. 1984). Inman et al. (1984) demonstrated that di-n-butyl phthalate in soil was completely degraded under both aerobic and anaerobic conditions within 100 days.

Johnson et al. (1977) evaluated the degradation of di-n-butyl phthalate by a variety of soil microorganisms. A number of species degraded di-n-butyl phthalate only to the monoester, while others degraded the monoester to phthalic acid. Some microorganisms also altered phthalic acid, probably via ring hydroxylation. The hydrolysis of the monoester appeared to be the most difficult step. These data indicate that degradation is likely to be most extensive in a mixed microbial population.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Di-n-butyl phthalate is globally distributed in the air. Di-n-butyl phthalate levels of approximately 1 ng/m^3 have been detected over the Pacific and Atlantic Oceans (Atlas and Giam 1981; Giam et al. 1980). Over New York City, di-n-butyl phthalate levels of 3.3 to 5.7 ng/m^3 have been detected (Bove et al. 1978), and in industrialized areas along the Niagara River, levels of 4.5 ng/m^3 as vapor and 6.2 ng/m^3 as particulate have been reported (Hoff and Chan 1987).

The air from rooms recently covered with polyvinyl chloride tiles contained 150,000 to 260,000 ng/m^3 phthalate esters (EPA 1980b). High levels of di-n-butyl phthalate could also be present in enclosed rooms in which products such as white glue or nail polish were being used, but no data on actual concentrations of di-n-butyl phthalate in indoor air were located.

5.4.2 Water

Overall there appears to be considerable uniformity in the concentration of di-n-butyl phthalate in the surface waters of the United States, if locally contaminated areas are excluded. Water samples taken along the Mississippi River at the origin of the river in Minnesota, at the junction of the Ohio River, below Memphis, Tennessee, and just below New Orleans, had di-n-butyl phthalate concentration of 0.15, 0.14, 0.15 and 0.14 μg/L, respectively (DeLeon et al. 1986). There was no apparent effect of input from cities, industrial sources, or tributaries along the length of the river. These data suggest that transport mechanisms rather than source factors play a major role in distribution of di-n-butyl phthalate. This observation is consistent with the continuous extensive wet and dry deposition from air (see Section 5.3.1). At one site, Delaware River water contained 0.6 μg/L of di-n-butyl phthalate that could be traced to industrial sources (Sheldon and Hites 1979), but further downstream concentrations were considerably lower (0.1 to 0.4 μg/L).

Concentrations of di-n-butyl phthalate in water from the Inner Harbor Navigation Canal (which connects Lake Ponchartrain to the Mississippi River near New Orleans) were 0.5 to 0.7 μg/L (McFall et al. 1985b). These values are somewhat higher than found in the open river, but may relate to the more impounded nature of the lake.

The results of a 10 city drinking water survey indicated the presence of di-n-butyl phthalate in 6 of 10 city water supplies. Levels ranged from 0.1 to 0.2 μg/L for 5 cities, and was 5.0 μg/L for one city (Keith et al. 1976).

Data from the Contract Laboratory Program (CLP) Statistical Database (CLPSD 1988) indicated that di-n-butyl phthalate was detected in surface water at 77 of 862 hazardous waste sites being investigated under Superfund. The median concentration was 6 μg/L. Di-n-butyl phthalate was detected in groundwater at 90 of 862 sites, with a median concentration of 5 μg/L.

5.4.3 Soil

Most of the analytical data available for soils are on sediments or sludges. Considerable variability is encountered. In a study of sediments from Los Angeles Sanitation District's sewage outfalls, di-n-butyl phthalate was reported at 5 sites with concentrations ranging from 118 to 355 μg/kg dry weight (Swartz et al. 1983). Similar values were obtained along the Detroit River. Detectable di-n-butyl phthalate concentrations were reported in 4 of 13 samples, with values ranging from 190 to 650 μg/kg dry weight. Marine sediment from San Luis Pass, Texas, had approximately 15 to 93 μg/kg dry weight of di-n-butyl

phthalate (Murray et al. 1981). The CLP Statistical Database (1988) reported that di-n-butyl phthalate has been detected in soil at 115 of 862 hazardous waste sites sampled, with a median concentration of 440 µg/kg.

5.4.4 Other Media

Di-n-butyl phthalate may be used as a plasticizer for synthetic films used to wrap food products, and migration of di-n-butyl phthalate into food products may occur. Di-n-butyl phthalate may also enter food materials by uptake from the environment. For example, reported concentrations of di-n-butyl phthalate in fish ranged from 78 to 200 ppb (Giam and Wong 1987; Stalling et al. 1973; Williams 1973). Oyster and clam concentrations of di-n-butyl phthalate ranged from 40 to 570 ppb (McFall et al. 1985a; Ray et al. 1983). Ishida et al. (1981) reported the presence of di-n-butyl phthalate in egg white (but not in yolk) collected from six regions of Japan. Concentrations ranged from 50 to 150 ppb of di-n-butyl phthalate.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Table 5-1 summarizes estimated levels of exposure to di-n-butyl phthalate for members of the general population. It should be noted that the data used to estimate human exposure levels are mostly 10 or more years old so current exposure levels might be different, and that no reliable concentration measurements were located for foods other than fish. Based on these data, the highest exposure to di-n-butyl phthalate is most likely to come from food, possibly fish and seafood, with smaller amounts coming from air or water. Exposure to di-n-butyl phthalate via the dermal route would also be expected, but no data were available that could be used to estimate doses from dermal exposure to di-n-butyl phthalate. No data were located on typical exposure levels in the workplace, but it is likely they could be higher in certain cases than for the general population.

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Individuals who manufacture or use specialty plasticizers would have the highest potential for exposure to di-n-butyl phthalate. People living near chemical factories or hazardous waste sites where di-n-butyl phthalate is present could also have higher than average exposure.

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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-butyl phthalate is available. Where adequate

5. POTENTIAL FOR HUMAN EXPOSURE

TABLE 5-1. Estimated Levels of Human Exposure to Di-n-butyl Phthalate for Nonoccupational Exposure[a]

	Air	Water	Fish
Concentration in medium	0.003-0.006 $\mu g/m^3$ [b]	0.2 $\mu g/L$ [c]	78-200 $\mu g/kg$ [d]
Assumed rate of intake of medium	20 m^3/day	2 L/day	6.5 g/day
Assumed absorption fraction	0.5	0.9	0.9
Estimated dose ($\mu g/kg/day$)	0.0005-0.0009	0.005	0.007-0.02

[a]All calculations assume a 70-kg adult.
[b]Bove et al. 1978; Hoff and Chan 1987.
[c]Keith et al. 1986.
[d]Giam and Wong 1987; Stalling et al. 1973; Williams 1973.

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-butyl phthalate.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. 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. Data are available on the physical and chemical properties of di-n-butyl phthalate (see Chapter 3), and further research in this area does not appear to be essential.

Production, Use, Release, and Disposal. Available data indicate that di-n-butyl phthalate is produced in substantial amounts at several locations in the United States, is widely used in a variety of consumer products, and is subject to regulations concerning disposal. However, in the specialty plasticizer market, the amounts of specific plasticizers used in various applications often changes over time. Authoritative sources of current data on imports, exports, specific uses, releases to environmental media, and disposal methods were not located. Collecting such data would be valuable in estimating human exposure to di-n-butyl phthalate.

According to the Emergency Planning and Community Right to Know Act of 1986 (EPCRTKA), (§313), (Pub. L. 99-499, Title III, §313), industries are required to submit release information to the EPA. The Toxic Release Inventory (TRI), which contains release information for 1987, became available in May of 1989. This database will be updated yearly and should provide a more reliable estimate of industrial production and emission.

Environmental Fate. Although environmental fate is known to some extent, there are still major gaps in our understanding of partitioning and transport of di-n-butyl phthalate in the atmosphere as vapor and particulate. The volatility of di-n-butyl phthalate from water is unclear from the literature data. Little information is available on the reactions of di-n-butyl phthalate in the atmosphere. Further studies on these subjects would be helpful in improving models to predict the dispersion and persistence of di-n-butyl phthalate in the environment.

Bioavailability from Environmental Media. Exposure of the general public occurs via air, water, food supply, cosmetics and soils. However, the bioavailability of di-n-butyl phthalate in each of these media has not been investigated. Data of this type, especially on the availability by the inhalation, oral, and dermal routes of di-n-butyl phthalate bound to soils, sediments and air particulates, would be valuable in assessing the relative importance of these media to human exposure.

Food Chain Bioaccumulation. Available data indicate that di-n-butyl phthalate tends to be taken up and metabolized by invertebrates and fish, but there are no data on biomagnification through the food chain. Studies to obtain data of this sort would be useful in relating environmental levels to potential human exposure via the food supply.

Exposure Levels in Environmental Media. Information on exposure levels in the environment are relatively sparse. Although a number of atmospheric air levels have been reported, it would be useful to know more specifics about urban air levels. More extensive data on food and drinking water levels of di-n-butyl phthalate would also be useful in assessing total human exposure.

Exposure Levels in Humans. Few data are available on human tissue levels of di-n-butyl phthalate, so it is not possible at this time to assess the total impact of di-n-butyl phthalate on the human population. More information relating exposure levels to levels in humans would be valuable in assessing risks to populations surrounding hazardous waste sites.

Exposure Registries. No exposure registries for di-n-butyl phthalate were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

No information was located regarding on-going studies on the environmental fate and transport of di-n-butyl phthalate or on levels of human exposure to di-n-butyl phthalate.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring di-n-butyl phthalate in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify di-n-butyl phthalate. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect di-n-butyl phthalate in environmental samples are the methods approved by federal agencies 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 a trade association such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

Di-n-butyl phthalate may be determined by high resolution gas chromatography with an electron capture detector (HRGC/ECD) (Thuren 1986), gas chromatography/mass spectrometry (GC/MS) (Ching et al. 1981a; Ho 1983), high resolution gas chromatography/mass spectrometry (HRGC/MS) (Stanley 1986), or high resolution gas chromatography/Fourier transform infrared spectrometry (HRGC/FTIR) (EPA 1986d). Prior to analysis, di-n-butyl phthalate must be separated from the biological or environmental sample matrix and prepared in a form suitable for introduction into the analytical instrument. Methods for extracting di-n-butyl phthalate from biological materials and environmental samples are discussed below.

6.1 BIOLOGICAL MATERIALS

Since di-n-butyl phthalate is relatively non-volatile and lipophilic, most methods for separating it from biological materials involve extraction into an organic solvent such as ether, heptane or acetonitrile. In most cases, the material is homogenized in the solvent to improve extraction efficiency. Additional sample clean-up steps may be required to separate fats and other endogenous lipophilic materials that co-extract from the biological material (Walters 1988). Several analytical methods for the determination of di-n-butyl phthalate in biological materials are summarized in Table 6-1.

6.2 ENVIRONMENTAL SAMPLES

Separation of di-n-butyl phthalate from environmental samples such as water, soil, sediment or wastes is also usually accomplished through extraction with an organic solvent. In some cases, di-n-butyl phthalate may be separated without solvents by adsorption onto a suitable polymer

TABLE 6-1. Analytical Methods for Determining Di-n-butyl Phthalate in Biological Materials

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy (% Recovery)	Reference
Aquatic organisms	Extract with acetonitrile and petroleum ether	HRGC/ECD	0.1 ng/g	68	Thuren 1986
Adipose tissue	Extraction, bulk lipid removal, Florisil fractionation	HRGC/MS	10 ng/g	No data	Stanley 1986
Blood serum	Extraction, bulk lipid removal, Florisil fractionation	HRGC/MS	10 ng/g	No data	Stanley 1986
Blood serum	Extraction with organic solvents (propanol, heptane)	GC/MS	No data	No data	Ching et al. 1981a
Cooked meat	Remove with nitrogen gas trap, extract with diethyl ether	GC/MS	No data	No data	Ho 1983

HRGC = High resolution gas chromatography; ECD = electron capture detector; MS = mass spectrometry; GC = gas chromatography.

such as Tenax (Pankaw et al. 1988). Analytical methods for the determination of di-n-butyl phthalate in environmental samples are given in Table 6-2.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, 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-butyl phthalate 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-butyl phthalate.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. 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. Sensitive and selective methods using high resolution gas chromatography are available for the qualitative and quantitative measurement of parent di-n-butyl phthalate after it is separated from the biological matrix of tissue or fluid. However, methods for recovery of di-n-butyl phthalate from such samples have not been extensively developed, and additional work to improve and standardize sample extraction and preparation methods for biological fluids and tissues would be valuable in providing quantitative information concerning human exposure. The sensitivity of existing methods may not be high enough to measure background levels in the population, since an existing study failed to detect di-n-butyl phthalate in several samples (Stanley 1986). Because of the widespread use of di-n-butyl phthalate in laboratory equipment, cosmetics, and other consumer products, studies to determine background levels in the population must be done with care to avoid false positives from inadvertent contamination. Since health effects occur only after high levels of exposure, existing methods are probably capable of measuring body levels at which effects would be expected to occur in humans. The same method of high resolution gas chromatography could be adapted to measure body levels of metabolites of di-n-butyl phthalate, primarily monobutyl phthalate, which have the potential to be biomarkers of exposure.

TABLE 6-2. Analytical Methods for Determining Di-n-butyl Phthalate in Environmental Samples

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Air	Adsorption/solvent extraction with polyurethane foam plug	HRGC/MS	No data	115±5%[a]	Ligocki and Pankow 1985
Rainwater	Adsorb on Tenax-GC columns, thermally desorb	GC/MS	<34 ng/L	No data	Ligocki et al. 1985
Water	Extract with dichloromethane, exchange to hexane, concentrate	GC/ECD	0.36 µg/L	80±6%[a]	EPA 1982a
Water	Extract with dichloromethane at pH 11 and 2, concentrate	GC/MS	2.5 µg/L	80±6%[a]	EPA 1982b
Water	Adsorb on small bed volume Tenax cartridges, thermally desorb	GC/MS	No data	No data	Pankow et al. 1988
Soil	Extract with dichloromethane, cleanup, exchange to hexane	GC/ECD	240 ng/kg	96%	EPA 1986a
Wastes, non-water miscible	Extract with dichloromethane, cleanup, exchange to hexane	GC/ECD	36 mg/kg	96%	EPA 1986a
Soil	Extract from sample, cleanup	GC/MS	1.7 mg/kg	96%	EPA 1986b
Wastes, non-water miscible	Extract from sample, cleanup	GC/MS	350 mg/kg	76%	EPA 1986b
Soil/sediment	Extract from sample, cleanup	HRGC/MS	660 µg/kg	76%	EPA 1986c
Wastes, non-water miscible	Extract from sample, cleanup	HRGC/MS	50 mg/kg	76%	EPA 1986c
Soil/sediment	Extract from sample, cleanup	HRGC/FTIR	10 µg/L[b]	No data	EPA 1986d
Wastes, non-water miscible	Extract from sample, cleanup	HRGC/FTIR	10 µg/L[b]	No data	EPA 1986d

[a]Relative recovery, percent, ± standard deviation.
[b]Identification limit. Detection limits for actual samples are several orders of magnitude higher depending upon the sample matrix and extraction procedure employed.

HRGC = high resolution gas chromatography; MS = mass spectrometry; GC = gas chromatography; ECD = electron capture detector; FTIR = Fourier transform infrared spectrometry.

6. ANALYTICAL METHODS

No information was located concerning biomarkers of effect of di-n-butyl phthalate. Studies undertaken to determine biomarkers of effect would be most useful if one component were to develop precise, accurate, reliable, and specific methods for measuring background levels of the biomarker of effect in the population as well as the levels at which health effects, if any, occur.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Good methods with adequate sensitivity and selectivity are available for detecting and quantifying di-n-butyl phthalate contamination in water, air, soil, and waste samples. Soil, water, and food are the media of most concern for human exposure to di-n-butyl phthalate. The basic method of extraction followed by high resolution gas chromatography has the potential to be sensitive enough to measure background levels of di-n-butyl phthalate and its degradation products in the environment, but care must taken to ensure that samples are representative, volumes are sufficient, contamination is avoided, preservation is adequate, and extraction and purification are complete. In measuring of background levels in environmental media, contamination can pose a particular problem because of the extensive use of di-n-butyl phthalate in products found in laboratories. Existing methods should be sufficiently sensitive to measure levels of di-n-butyl phthalate at which health effects might occur.

6.3.2 On-going Studies

Research is ongoing to develop a "Master Analytical Scheme" for organic compounds in water (Michael and Pellizzari 1988), which includes di-n-butyl phthalate as an analyte. The overall goal is to detect and quantitatively measure organic compounds at 0.1 μg/L in drinking water, 1 μg/L in surface waters, and 10 μg/L in effluent waters. Analytes are to include numerous nonvolatile compounds and some compounds that are only "semi-soluble" in water, as well as volatile compounds (bp<150°C).

Examination of the literature suggests that studies are underway to improve means for determining di-n-butyl phthalate in biological samples and environmental media. Improvements continue to be made in chromatographic separation and detection. Current high level activity in the areas of supercritical fluid extraction and supercritical fluid chromatography (Smith 1988) includes di-n-butyl phthalate in biological samples and environmental media as an analyte. Fourier transform infrared flow cell detectors are promising for this application (Wieboldt et al. 1988).

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in people if exposure were to occur, a number of regulations and guidelines have been established for di-n-butyl phthalate by various national and state agencies. These values are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Di-n-butyl Phthalate

Agency	Description	Value	Reference
	National		
Regulations:			
a. Air:			
OSHA	PEL TWA	5 mg/m^3	OSHA 1989 (29 CFR 1910.1000, Table 2-1-A)
b. Water:			
EPA OWRS	General permits under NPDES	No data	40 CFR 122 (Appendix D, Table II)
	General pretreatment regulations for existing and new sources of pollution	No data	40 CFR 403
c. Nonspecific media:			
EPA	Oral RfD	Subchronic 1mg/kg/day Chronic .1mg/kg/day	IRIS 1988
EPA OERR	Reportable quantity	10 lb	EPA 1985a, (40 CFR 302.4)
EPA OSW	Hazardous waste constituent (Appendix VIII)	No data	EPA 1980a, (40 CFR 261)
	Land disposal restrictions	No data	EPA 1988a, 1989b, (40 CFR 268)
	Groundwater monitoring list (Appendix IX)	No data	EPA 1987b, (40 CFR 264)
EPA OTS	Toxic chemical release reporting	No data	EPA 1988b, (40 CFR 372)
	Preliminary assessment information rule	No data	EPA 1982c, (40 CFR 712.30)
	Health and safety data reporting	No data	EPA 1988c, (40 CFR 716.120)
	Testing consent order (alkyl phthalates)	No data	EPA 1989c, (40 CFR 799.5000)
FDA	Use as a component of adhesives and coatings in food packaging	No data	21 CFR 175.105, 175.300, 175.380, 175.390
	Indirect food additive polymer	No data	21 CFR 177.1200 177.1210, 177.2420, 177.2600
	Indirect food additive: paper and paperboard component	Yes	21 CFR 176.170, 176.180, 176.300
Guidelines:			
a. Air:			
ACGIH	TLV TWA	5 mg/m^3	ACGIH 1986
NIOSH	IDLH	9300 mg/m^3	NIOSH 1985a

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Value	Reference
b. Water:			
EPA OWRS	Ambient water quality criteria		
	Ingesting water and organisms	34 mg/L	EPA 1980b
	Ingesting organisms only	154 mg/L	EPA 1980b
Other:			
EPA	Carcinogenic classification	Group D[a]	IRIS 1988
	State		
Regulations:			
a. Air:	Acceptable ambient air concentration		NATICH 1988
Connecticut		100 $\mu g/m^3$ (8 hr)	
Nevada		0.1190 mg/m^3 (8 hr)	
North Dakota		0.05 mg/m^3 (8 hr)	
		0.10 mg/m^3 (1 hr)	
Virginia		80 $\mu g/m^3$ (24 hr)	
b. Water:	Drinking water		FSTRAC 1988
Kansas		770 µg/L	
Maine		2200 µg/L	

[a]Group D = not classifiable.

OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; TWA = Time-Weighted Average; EPA = Environmental Protection Agency; OWRS = Office of Water Regulations and Standards; NPDES = National Pollutant Discharge Elimination System; OERR = Office of Emergency and Remedial Response; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; FDA = Food and Drug Administration; ACGIH = American Conference of Governmental Industrial Hygienists; TLV = Threshold Limit Value; NIOSH = National Institute for Occupational Safety and Health; IDLH = Immediately Dangerous to Life or Health Level; RfD = Reference Dose.

8. REFERENCES

Acey R, Healy P, Unger TF, et al. 1987. Growth and aggregation behavior of representative phytoplankton as affected by the environmental contaminant di-n-butyl phthalate. Bull Environ Contam Toxicol 39:1-6.

* ACGIH. 1986. Documentation of the threshold limit values and biological exposure indices. 5th ed. American Conference of Governmental Industrial Hygienists. Cincinnati, OH.

* Agarwal DK, Lawrence WH, Nunez LJ, et al. 1985. Mutagenicity evaluation of phthalic acid esters and metabolites in Salmonella typhimurium cultures. J Toxicol Environ Health 16:61-69.

* Al-Omran LA, Preston MR. 1987. The interactions of phthalate esters with suspended particulate material in fresh and marine waters. Environmental Pollution 46:177-186.

* Albaiges J, Casado F, Ventura F. 1986. Organic indicators of groundwater pollution by a sanitary landfill. Water Res 20:1153-1159.

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

* Atlas E, Giam CS. 1981. Global transport of organic pollutants: Ambient concentrations in the remote marine atmosphere. Science 211:163-165.

Atlas E, Velasco A, Sullivan K, et al. 1983. A radiotracer study of air-water exchange of synthetic organic compounds. Chemosphere 12:1251-1258.

Bakale G, McCreary RD. 1987. A physico-chemical screening test for chemical carcinogens: the k_e test. Carcinogenesis 8:253-264.

Barber ED, Astill BD, Moran EJ, et al. 1987. Peroxisome induction studies on seven phthalate esters. Toxicol Ind Health 3:7-22.

* Barber LB, Thurman EM, Schroeder MP, et al. 1988. Long-term fate of organic micropollutants in sewage-contaminated groundwater. Environ Sci Technol 22:205-211.

* = Cited in text.

8. REFERENCES

* Barnes D, Bellin J, DeRosa C, et al. 1987. Reference dose (RfD): description and use in health risk assessments. Volume I, Appendix A: Integrated risk information system supportive documentation. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Evironmental Assessment. EPA/600/8-86/032a.

Bedding ND, McIntyre AE, Perry R, et al. 1982. Organic contaminants in the aquatic environment: 1. Sources and occurrence. Sci Total Environ 25:143-167.

* Bell FP. 1982. Effects of phthalate esters on lipid metabolism in various tissues, cells and organelles in mammals. Environ Health Perspect 45:41-50.

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

* BIBRA. 1986. A 21 day feeding study of di-n-butyl phthalate to rats: Effects on the liver and lipids. Report to Chemical Manufacturers Association, Washington, DC, by the British Industrial Biological Research Association, Carshalton, Surrey, UK. CMA Reference PE 28.0-BT-BIB.

* Bove JL, Dalven P, Kukreja VP. 1978. Airborne di-butyl and di-(2-ethylhexyl)-phthalate at three New York City air sampling stations. Int J Environ Anal Chem 5:189-194.

Bove JL, Dalven P. 1981. A GC/MS method of determining airborne di-n-butyl- and di-(2-ethyl hexyl) phthalates. Int J Environ Anal Chem 10:189-196.

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.

Burmaster DE. 1982. The new pollution: Groundwater contamination. Environment 24:7-13, 33-36.

Cagianut B. 1954. Keratitis erosiva and nephritis toxica nach einnahme von dibutylphthalat. Schweiz Med Wochen 35:1243-1244. (German)

* Callahan MA, Slimak MW, Gabel NW, et al. 1979. Water-related environmental fate of 129 priority pollutants: Volume I: Introduction and technical background, metals and inorganics, pesticides and PCBs. Washington, DC: U.S. Environmental Protection Agency, Office of Water Planning and Standards. EPA-440/4-79-029a. NTIS No. PB 80-204373.

Calnan CD. 1975. Dibutyl phthalate. Contact Dermatitis 1:388.

8. REFERENCES

Cater BR, Cook MW, Gangolli SD. 1976. Zinc metabolism and dibutyl phthalate-induced testicular atrophy in the rat. Biochem Soc Trans 4:652-653.

* Cater BR, Cook MW, Gangolli SD, et al. 1977. Studies on dibutyl phthalate-induced testicular atrophy in the rat: Effect on zinc metabolism. Toxicol Appl Pharmacol 41:609-618.

CCTTE. 1988. Computerized Listing of Chemicals Being Tested for Toxic Effects. United Nations Environment Programme, International Programme on Chemical Safety, International Register of Potentially Toxic Chemicals, Geneva, Switzerland.

* Ching NP, Jham GN, Subbarayan C, et al. 1981a. Gas chromatographic-mass spectrometric detection of circulating plasticizers in surgical patients. J Chromatog 222:171-177.

Ching NP, Jham GN, Subbarayan C, et al. 1981b. Gas chromatographic quantitation of two plasticizers contaminating IV fluids stored in plastic containers. J Chromatog Biomed Appl 225:196-201.

Chrostek WJ, Moshell AN. 1984. Health hazard evaluation report no. HETA 81-275-1122, General Telephone Company, York, Pennsylvania. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

Clansky KB, ed. 1986. Chemical guide to the OSHA hazard communication standard. Burlingame, CA: Roytech Publications, Inc., 57, 653-656.

Clark JR, Patrick JM Jr, Moore JC, et al. 1987. Waterborne and sediment-source toxicities of six organic chemicals to grass shrimp *(Palaemonetes pugio)* and amphioxus *(Branchiostoma caribaeum)*. Arch Environ Contam Toxicol 16:401-407.

Clayton GD, Clayton FE. 1981. Patty's industrial hygiene and toxicology, third revised edition, volume 2A, toxicology. New York, NY: John Wiley and Sons, 2344-2347.

* CLPSD. 1988. Contract Laboratory Program Statistical Database. Viar and Company, Management Services Division, Alexandria, VA. December 22, 1988.

* Cosmetic Ingredient Review Committee. 1985. Final report on the safety assessment of dibutyl phthalate, dimethyl phthalate, and diethyl phthalate. Journal of the American College of Toxicology 4:267-303.

8. REFERENCES

Cote MG, Plaa GL, Valli VE, et al. 1985. Subchronic effects of a mixture of "persistent" chemicals found in the Great Lakes. Bull Environ Contam Toxicol 34:285-290.

* Cripe CR, Walker WW, Pritchard PH, et al. 1987. A shake-flask test for estimation of biodegradability of toxic organic substances in the aquatic environment. Ecotoxicol Environ Safety 14:239-251.

Cummings AM, Gray LE Jr. 1987. Dibutyl phthalate: maternal effects versus fetotoxicity. Toxicol Lett 39:43-50.

Daniel JW. 1978. Toxicity and metabolism of phthalate esters. Clin Toxicol 13:257-268.

Daniel JW. 1979. Toxicity and metabolism of phthalate esters. In: Winek L, Shanor SP, eds. Toxicology annual: Vol. 3. New York, NY: Marcel Dekker, Inc., 257-268.

* DeFoe DL, Holcombe GW, Hammermeister DE, et al. 1990. Solubility and toxicity of eight phthalate esters to four aquatic organisms. Env Toxicol Chem 9:623-636.

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

Eaton RW, Ribbons DW. 1982. Metabolism of dibutyl phthalate and phthalate by Micrococcus sp. strain 12B. J Bacteriol 151:48-57.

* Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15:30-38.

Ekwall B, Nordensten C, Albanus L. 1982. Toxicity of 29 plasticizers to HeLa cells in the MIT-24 system. Toxicology 24:199-210.

* Elsisi AE, Carter DE, Sipes IG. 1989. Dermal absorption of phthalate diesters in rats. Fundam Appl Toxicol 12:70-77.

* Engelhardt G, Wallnofer PR, Hutzinger O. 1975. The microbial metabolism of di-n-butyl phthalate and related dialkyl phthalates. Bull Environ Contam Toxicol 13:342-347.

* Engelhardt G, Wallnofer PR. 1978. Metabolism of di- and mono-n-butyl phthalate by soil bacteria. Appl Environ Microbiol 35:243-246.

* EPA. 1980a. U.S. Environmental Protection Agency. Federal Register. 45:33084-33133.

8. REFERENCES

* EPA. 1980b. Ambient water quality criteria for: Phthalate esters. Washington, DC: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. EPA-440/5-80-067. NTIS No. PB81-117780.

* EPA. 1982a. Test method: Phthalate esters-method 606. In: Longbottom JE, Lichtenberg JJ, eds. Test methods: Methods for organic chemical analysis of municipal and industrial wastewater. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. EPA-600/4-82-057.

* EPA. 1982b. Test method: Base/neutrals and acids-method 625. In: Longbottom JE, Lichtenberg JJ, eds. Test methods: Methods for organic chemical analysis of municipal and industrial wastewater. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory. EPA-600/4-82-057.

* EPA. 1982c. U.S. Environmental Protection Agency. Federal Register. 47:26992-27008.

EPA. 1983a. Reportable quantity document for 1,2-benzene dicarboxylic acid, dibutyl ester (dibutyl phthalate). Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response. External Review Draft. ECAO-CIN-R039.

EPA. 1983b. Treatability manual: Volume I. Treatability data. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/2-82-001a.

* EPA. 1985. U.S. Environmental Protection Agency: Part II. Federal Register. 50:13456-13522.

* EPA. 1986a. Method 8060: Phthalate esters. In: Test methods for evaluating solid waste. 3rd ed. SW-846. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

* EPA. 1986b. Method 8250: Gas chromatography/mass spectrometry for semivolatile organics: packed column technique. In: Test methods for evaluating solid waste. 3rd ed. SW-846. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

* EPA. 1986c. Method 8270: Gas chromatography/mass spectrometry for semivolatile organics: capillary column technique. In: Test methods for evaluating solid waste. 3rd ed. SW-846. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

8. REFERENCES

* EPA. 1986d. Method 8410: capillary column analysis of semivolatile organic compounds by gas chromatography/fourier transform infrared (GC/FT-IR) spectrometry. In: Test methods for evaluating solid waste. 3rd ed. SW-846. Washington, DC: U.S. Environmental Protection Agency Office of Solid Waste and Emergency Response.

EPA. 1987a. U.S. Environmental Protection Agency: Part II. Federal Register. 52:13378-13410.

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

EPA. 1987c. Health effects assessment for selected phthalic acid esters. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. EPA/600/8-88/053. NTIS No. PB88-178934.

EPA. 1987d. U.S. Environmental Protection Agency. Federal Register. 52:48073-48074.

* EPA. 1988a. U.S. Environmental Protection Agency: Part II. Federal Register. 53:31138-31222.

* EPA. 1988b. U.S. Environmental Protection Agency: Part II. Federal Register. 53:4500-4539.

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

* EPA. 1989a. Interim Methods for Development of Inhalation References Doses. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. Washington, DC. EPA 600/8-88/066F.

* EPA. 1989b. U.S. Environmental Protection Agency: Part II. Federal Register. 54:1056-1120.

* EPA. 1989c. U.S. Environmental Protection Agency. Federal Register. 54:618-621.

Fallon ME, Horvath FJ. 1985. Preliminary assessment of contaminants in soft sediments of the Detroit River. J Great Lakes Res 11:373-378.

* Feiler HD, Storch PJ, Southworth R. 1980. Organics in municipal sludges survey of forty cities. Natl Conf Munic Ind Sludge Util Disposal [Pap.] 53-57.

8. REFERENCES

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

Fishbein L. 1984. Toxicity of the components of styrene polymers: polystyrene, acrylonitrile-butadiene-styrene (ABS) and styrene-butadiene-rubber (SBR). Reactants and additives. In: Jarvisalo J, Pfaffli P, Vainio H, eds. Industrial hazards of plastics and synthetic elastomers. New York, NY: Alan R. Liss, Inc., 239-262.

* Florin I, Rutberg L, Curvall M, et al. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 18:219-232.

* 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.

Foster PM, Lake BG, Cook MW, et al. 1981. Structure-activity requirements for the induction of testicular atrophy by butyl phthalates in immature rats: effect on testicular zinc content. In: Snyder R, Parke DV, Kocsis JJ, et al., eds. Biological reactive intermediates-II: Chemical mechanisms and biological effects, Part A. New York, NY: Plenum Press, 445-452.

* Foster PM, Cook MW, Thomas LV, et al. 1982. Differences in urinary metabolic profile from di-n-butyl phthalate-treated rats and hamsters: A possible explanation for species differences in susceptibility to testicular atrophy. Drug Metab Dispos 11:59-61.

* FSTRAC. 1988. Summary of state and federal drinking water standards and guidelines. Washington, DC: Federal-State Toxicology and Regulatory Alliance Committee, Chemical Communication Subcommittee.

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

Geissert JO. 1977. Technical assistance report no. TA-76-66, Mr. Gary Armstrong, Cincinnati, Ohio. Cincinnati, OH: National Institute for Occupational Safety and Health. NTIS No. PB82-189747.

Gesler RM. 1973. Toxicology of di-2-ethylhexyl phthalate and other phthalic-acid ester plasticizers. Environ Health Perspect 3:73-79.

Giam CS, Chan HS, Neff GS. 1978a. Phthalate ester plasticizers, DDT, DDE and polychlorinated biphenyls in biota from the Gulf of Mexico. Marine Pollution Bulletin 9:249-251.

8. REFERENCES

Giam CS, Chan HS, Neff GS, et al. 1978b. Phthalate ester plasticizers: A new class of marine pollutant. Science 199:419-421.

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

* Giam CS, Atlas E, Chan HS, et al. 1980. Phthalate esters, PCB and DDT residues in the Gulf of Mexico atmosphere. Atmospheric Environment 14:65-69.

Gosselin RE, Smith RP, Hodge HC, et al, eds. 1984. Clinical toxicology of commercial products. 5th ed. Baltimore, MD: Williams and Wilkins, II-204.

Gothe R. 1974. Oxidation with tetrabutylammonium permanganate for quantitation of DDT residues in GLC determination of chlorinated hydrocarbons. Bull Environ Contam Toxicol 11:451-455.

Gray TJ, Gangolli SD. 1986. Aspects of the testicular toxicity of phthalate esters. Environ Health Perspect 65:229-235.

* Gray TJ, Rowland IR, Foster PM, et al. 1982. Species differences in the testicular toxicity of phthalate esters. Toxicol Lett 11:141-147.

Green DR, Le Pape D. 1987. Stability of hydrocarbon samples on solid-phase extraction columns. Anal Chem 59:699-703.

Haley TJ. 1975. Vinyl chloride: How many unknown problems? J Toxicol Environ Health 1:47-73.

Hall DE, Austin P, Fairweather FA. 1966. Acute (mouse and rat) and short-term (rat) toxicity studies on dibutyl(diethylene glycol bisphthalate). Food Cosmet Toxicol 4:383-388.

* Hannah SA, Austern BM, Eralp AE, et al. 1986. Comparative removal of toxic pollutants by six wastewater treatment processes. J Water Pollut Control Fed 58:27-34.

Hannah SA, Austern BM, Eralp AE, et al. 1988. Removal of organic toxic pollutants by trickling filter and activated sludge. J Water Pollut Control Fed 60:1281-1283.

* Hardin BD. 1987. A recommended protocol for the Chernoff/Kavlock preliminary developmental toxicity test and a proposed method for assigning priority scores based on results of that test. Teratogenesis Carcinogen Mutagen 7:85-94.

8. REFERENCES

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

Harsanyi BB, Foong WC, Jones DW. 1988. Implantation of denture soft polymers into hamster cheek pouch [Abstract]. J Dent Res 67:263.

Hauser TR, Bromberg SM. 1982. EPA's monitoring program at Love Canal 1980. Environmental Monitoring and Assessment 2:249-271.

Hawker DW, Connell DW. 1986. Bioconcentration of lipophilic compounds by some aquatic organisms. Ecotoxicol Environ Safety 11:184-197.

* Hawthorne SB. 1988. 1988 workshop on supercritical fluid chromatography. American Laboratory (August 1988):6-8.

* Hazleton Biotechnologies. 1986. Mutagenicity of IC in a mouse lymphoma mutation assay: Final report. Hazleton Biotechnologies Company, Kensington, MD. HB Project No. 20989.

* Ho CT, Lee KN, Jin QZ. 1983. Isolation and identification of volatile flavor compounds in fried bacon. J Agric Food Chem 31:336-342.

* Hoff RM, Chan KW. 1987. Measurement of polycyclic aromatic hydrocarbons in the air along the Niagara River. Environ Sci Technol 21:556-561.

Hollett BA. 1977. Health hazard evaluation/toxicity determination report 76-92-363, Jeffery Bigelow Design Group, Inc., Washington, DC. Cincinnati, OH: National Institute for Occupational Safety and Health. NIOSH-TR-HHE-76-92-36. NTIS NO. PB-273913.

* Howard PH. 1989. Handbook of environmental fate and exposure data of environmental chemicals. Vol. 1. Large production and priority pollutants. Chelsea, MA: Lewis Publishing Inc., 217-228.

* Howard PH, Banerjee S, Robillard KH. 1985. Measurement of water solubilities, octanol/water partition coefficients and vapor pressures of commercial phthalate esters. Environ Toxicol Chem 4:653-661.

* HSDB. 1988. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD. December 1988.

Hudson VW. 1982. TSCA interagency testing committee actions related to phthalates. Environ Health Perspect 45:135-136.

8. REFERENCES

Hudson RA, Austerberry CF, Bagshaw JC. 1981. Phthalate ester hydrolases and phthalate ester toxicity in synchronously developing larvae of the brine shrimp (Artemia). Life Sci 29:1865-1872.

Husain SL. 1975. Dibutyl phthalate sensitivity. Contact Dermatitis 1:395.

Hutchins SR, Tomson MB, Ward CH. 1983. Trace organic contamination of ground water from a rapid infiltration site: A laboratory-field coordinated study. Environ Toxicol Chem 2:195-216.

* Inman JC, Strachan SD, Sommers LE, et al. 1984. The decomposition of phthalate esters in soil. J Environ Sci Health B19:245-257.

* Inouye B, Ogino Y, Ishida T, et al. 1978. Effects of phthalate esters on mitochrondrial oxidative phosphorylation in the rat. Toxicol Appl Pharmacol 43:189-198.

* IRIS. 1988. Integrated Risk Information System. U.S. Environmental Protection Agency, Washington, DC. December 1988.

IRPTC. 1989. IRPTC data profile on: Dibutyl phthalate. International Register of Potentially Toxic Chemicals, United Nations Environment Programme, Geneva, Switzerland. January 1989.

* Ishida M, Suyama K, Adachi S. 1981. Occurrence of dibutyl and di(2-ethylhexyl) phthalate in chicken eggs. J Agric Food Chem 29:72-74.

* Ishidate M Jr, Odashima S. 1977. Chromosome tests with 134 compounds on Chinese hamster cells in vitro - A screening for chemical carcinogens. Mutat Res 48:337-353.

Jansson B, Jensen S, Olsson M, et al. 1975. Identification by GC-MS of phenolic metabolites of PCB and p,p'-DDE isolated from Baltic guillemot and seal. Ambio 4:93-97.

John JA, Wroblewski DJ, Schwetz BA. 1984. Teratogenicity of experimental and occupational exposure to industrial chemicals. Issues and Reviews in Teratology 2:267-324.

* Johnson BT, Heitkamp MA, Jones JR. 1984. Environmental and chemical factors influencing the biodegradation of phthalic acid esters in freshwater sediments. Environmental Pollution (Series B) 8:101-118.

8. REFERENCES

* Johnson BT, Stalling DL, Hogan JW, et al. 1977. Dynamics of phthalic acid esters in aquatic organisms. In: Suffet IH, ed. Fate of pollutants in the air and water environments: Part 2. Chemical and biological fate of pollutants in the environment. New York, NY: John Wiley and Sons, 283-300.

Johnson EM, Gabel BE. 1983. An artificial embryo for detection of abnormal developmental biology. Fundam Appl Toxicol 3:243-249.

Johnson EM, Newman LM, Gabel BE, et al. 1988. An analysis of the Hydra assay's applicability and reliability as a developmental toxicity prescreen. Journal of the American College of Toxicology 7:111-126.

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

Jury WA, Winer AM, Spencer WF, et al. 1987. Transport and transformations of organic chemicals in the soil-air-water ecosystem. Rev Environ Contam Toxicol 99:119-164.

Kamiya A, Ose Y. 1987. Mutagenic activity and PAH analysis in municipal incinerators. Sci Total Environ 61:37-49.

Kaneshima H, Yamaguchi T, Okui T, et al. 1978. Studies on the effects of phthalate esters on the biological system (Part 2) In vitro metabolism and biliary excretion of phthalate esters in rats. Bull Environ Contam Toxicol 19:502-509.

Kaneshima H, Yamaguchi T, Itoh K. 1978. Studies on the effects of phthalate esters on the biological system: (Part 3). The in vitro metabolism of dibutyl phthalate in the small intestines of rats. Bull Environ Contam Toxicol 20:725-728.

Kawamura K, Kaplan IR. 1983. Organic compounds in the rainwater of Los Angeles. Environ Sci Technol 17:497-501.

* Kawano M. 1980a. Toxicological studies on phthalate esters. I. Inhalation effects of dibutyl phthalate (DBP) on rats. Nippon Eiseigaku Zasshi (Jpn J Hyg) 35:684-692. (Japanese) (English translation)

* Kawano M. 1980b. Toxicological studies on phthalate esters. II. Metabolism, accumulation and excretion of phthalate esters in rats. Nippon Eiseigaku Zasshi (Jpn J Hyg) 35:693-701. (Japanese) (English translation)

* Kawashima Y, Hanioka N, Matsumura M, et al. 1983. Induction of microsomal stearoyl-CoA desaturation by the administration of various peroxisome proliferators. Biochim Biophys Acta 752:259-264.

8. REFERENCES

* Keith LH, Garrison AW, Allen FR, et al. 1976. Identification of organic compounds in drinking water from thirteen U.S. cities. In: Keith LH, ed. Identification and analysis of organic pollutants in water. Ann Arbor, MI: Ann Arbor Science Publishers, Inc., 329-362.

Kerster HW, Schaeffer DJ. 1983. Brine shrimp (Artemia Salina) Nauplii as a teratogen test system. Ecotoxicol Environ Safety 7:342-349.

* Killinger JM, Basaran AH, Persing RL, et al. 1988a. Maximum perinatal dose feed study of dibutyl phthalate (CAS No. 84-74-2) in Fischer 344 rats. Report to National Toxicology Program, Research Triangle Park, NC by Battelle, Columbus, OH.

* Killinger JM, Basaran AH, Mezza LE, et al. 1988b. Prechronic dosed feed study of dibutyl phthalate (CAS No. 84-74-2) in B6C3F, mice (phase I - maximum perinatal dose). Report to National Toxicology Program, Research Triangle Park, NC, by Battelle, Columbus, OH.

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

Kool HJ, van Kreijl CF, Zoeteman BC. 1982. Toxicology assessment of organic compounds in drinking water. CRC Crit Rev Environ Control 12:307-357.

Korhonen A, Hemminki K, Vainio H. 1983. Embryotoxic effects of phthalic acid derivatives, phosphates and aromatic oils used in the manufacturing of rubber on 3 day chicken embryos. Drug Chem Toxicol 6:191-208.

* Krauskopf LG. 1973. Studies of the toxicity of phthalates via ingestion. Environ Health Perspect 3:61-72.

Kurane R. 1986. Microbial degradation of phthalate esters. Microbiological Sciences 3:92-95.

* Kurane R, Suzuki T, Takahara Y. 1979. Microbial population and identification of phthalate ester-utilizing microorganisms. Agric Biol Chem 43:907-917.

* 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.

* Lamb JC, Chapin RE, Teague J, et al. 1987. Reproductive effects of four phthalic acid esters in the mouse. Toxicol Appl Pharmacol 88:255-269.

8. REFERENCES

Lao RC, Oja H, Thomas RS, et al. 1973. Assessment of environmental problems using the combination of gas chromatography and quadrupole mass spectrometry. Sci Total Environ 2:223-233.

Lawrence WH, Malik M, Turner JE, et al. 1975. A toxicological investigation of some acute, short-term, and chronic effects of administering di-2-ethylhexyl phthalate (DEHP) and other phthalate esters. Environ Res 9:1-11.

Layton DW, McKone TE, Hall CH, et al. 1986. Demilitarization of conventional ordnance: Priorities for data-base assessments of environmental contaminants. Fort Detrick, Federick, MD: U.S. Army Medical Research and Development Command. ADA 182922.

Layton DW, Mallon BJ, Rosenblatt DH, et al. 1987. Deriving allowable daily intakes for systemic toxicants lacking chronic toxicity data. Regul Toxicol Pharmacol 7:96-112.

LeFaux R. 1968. Practical toxicology of plastics. Cleveland, OH: The Chemical Rubber Co., 137-138, 346-349, 412-419.

* Lehman AJ. 1955. Insect repellents. Quarterly Bulletin 19:87-99.

* Ligocki MP, Pankow JF. 1985. Assessment of absorption/solvent extraction with polyurethane foam and adsorption/thermal desorption with Tenax-GC for the collection and analysis of ambient organic vapors. Anal Chem 57:1138-1144.

* Ligocki MP, Leuenberger C, Pankow JF. 1985. Trace organic compounds in rain-II. Gas scavenging of neutral organic compounds. Atmos Environ 19:1609-1617.

* Litton Bionetics. 1985a. Evaluation of IC in the in vitro transformation of BALB/3T3 cells assay: Final Report. Report to Chemical Manufacturers Association, Washington, DC by Litton Bionetics, Inc. Kensington, MD. LBI Project No. 20992.

Litton Bionetics. 1985b. Evaluation of IC in the mouse lymphoma toxicity assay: Final report. Report to Chemical Manufacturers Association, Washington, DC by Litton Bionetics, Inc. Kensington, MD. LBI Project No. 20989.

Lock EA, Mitchell AM, Elcombe CR. 1989. Biochemical mechanisms of induction of hepatic peroxisome proliferation. Ann Rev Pharmacol Toxicol 29:145-163.

8. REFERENCES

Lucas SV. 1984. GC/MS analysis of organics in drinking water concentrates and advanced waste treatment concentrates: Volume I: Analysis results for 17 drinking water, 16 advanced waste treatment and 3 process blank concentrates. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development. EPA-600/1-84-020a. NTIS No. PB85-128221.

* Mabey WR, Smith JH, Podoll RT, et al. 1982. Aquatic fate process data for organic priority pollutants. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA 440/4-81-014.

* McFall JA, Antoine, SR, DeLeon IR. 1985a. Base-neutral extractable organic pollutants in biota and sediments from Lake Pontchartrain. Chemosphere 14:1561-1569.

* McFall JA, Antoine SR, DeLeon IR. 1985b. Organics in the water column of Lake Pontchartrain. Chemosphere 14:1253-1265.

* Melnick RL, Schiller CM. 1985. Effect of phthalate esters on energy coupling and succinate oxidation in rat liver mitochondria. Toxicology 34:13-27.

* Mes J, Coffin DE, Campbell DS. 1974. Di-n-butyl and di-2-ethylhexyl phthalate in human or adipose tissue. Bull Environ Contam Toxicol 12:721-725.

* Michael LC, Pellizari ED. 1988. Development and evaluation of a procedure for determining volatile organics in water. Environ Sci Technol 22:565-570.

* Milkov LE, Aldyreva MV, Popoua TB, et al. 1973. Health status of workers exposed to phthalate plasticizers in the manufacture of artificial leather and films based on PVC resins. Env Hlth Perspect 3:175-178.

Morrissey RE, Lamb JC, Schwetz BA, et al. 1988. Association of sperm, vaginal cytology, and reproductive organ weight data with results of continuous breeding reproduction studies in Swiss (CD-1) mice. Fundam Appl Toxicol 11:359-371.

* Murakami K, Nishiyama K, Higuti T. 1986a. Toxicity of dibutyl phthalate and its metabolites in rats. Nippon Eiseigaku Zasshi (Jpn J Hyg) 41:775-781.

* Murakami K, Nishiyama K, Higuti T. 1986b. Mitochondrial effect of orally administered dibutyl phthalate in rats. Nippon Eiseigaku Zasshi (Jpn J Hyg) 41:769-774.

8. REFERENCES

* Murature DA, Tang SY, Steinhardt G, et al. 1987. Phthalate esters and semen quality parameters. Biomed Environ Mass Spectrom 14:473-477.

* Murray HE, Ray LE, Giam CS. 1981. Analysis of marine sediment, water and biota for selected organic pollutants. Chemosphere 10:1327-1334.

NAS. 1977. Drinking water and health. Washington, DC: National Academy of Sciences.

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

* NATICH. 1988. NATICH data base report on state, local and EPA air toxics activities. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, National Air Toxics Information Clearinghouse. EPA-450/5-88-007. NTIS No. PB 89-106983.

Natusch DF, Tomkins BA. 1978. Isolation of polycyclic organic compounds by solvent extraction with dimethyl sulfoxide. Anal Chem 50:1429-1434.

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

* Nikonorow M, Mazur H, Piekacz H. 1973. Effect of orally administered plasticizers and polyvinyl chloride stabilizers in the rat. Toxicol Appl Pharmacol 26:253-259.

* NIOSH. 1985a. NIOSH pocket guide to chemical hazards. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

NIOSH. 1985b. Dibutyl phthalate and di(2-ethylhexyl) phthalate - method 5020. In: NIOSH manual of analytical methods. 3rd ed. Cincinnati, OH: National Institute for Occupational Safety and Health.

NIOSH. 1988a. National occupational exposure survey. Cincinnati, OH: National Institute for Occupational Safety and Health.

NIOSH. 1988b. National occupational hazard survey. Cincinnati, OH: National Institute for Occupational Safety and Health.

* NLM. 1988. Chemline. National Library of Medicine, Bethesda, MD. December 1988.

8. REFERENCES

Norpoth K. 1983. Phthalates. In: Parmeggiani L, ed. Encyclopaedia of occupational health and safety. 3rd ed. Vol. 2. Geneva, Switzerland: International Labour Office, 1690-1693.

* Nyssen GA, Miller ET, Glass TF, et al. 1987. Solubilities of hydrophobic compounds in aqueous-organic solvent mixtures. Environmental Monitoring and Assessment 9:1-11.

* O'Grady DP, Howard PH, Werner AF. 1985. Activated sludge biodegradation of 12 commercial phthalate esters. Appl Environ Microbiol 49:443-445.

Oehme M. 1985. Negative ion chemical ionization mass spectrometry--A useful technique for the selective detection of polar substituted polycyclic aromatic hydrocarbons with mutagenic properties. Chemosphere 14:1285-1297.

Ohta Y, Nakamoto M. 1979. Metabolism of di-n-butyl phthalate by Aeromomonas Sp. Hakko Kogaku Kaishi 57:50-53.

* Oishi S, Hiraga K. 1980a. Effect of phthalic acid esters on mouse testes. Toxicol Lett 5:413-416.

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

Okada S, Tamemasa O. 1978. [Distribution and metabolism of di-(n-butyl)-phthalate in mice and its interaction with nucleic acids and proteins.] Yakugaku Zasshi 98:1229-1235. (Japanese)

* OSHA. 1989. U.S. Department of Labor. Occupational Safety and Health Administration: Part III. Federal Register. 54:2332-2983.

Overcash MR, Weber JB, Miles ML. 1982. Behavior of organic priority pollutants in the terrestrial system: Di-n-butyl phthalate ester, toluene, and 2,4-dinitrophenol. Raleigh, NC: North Carolina State University, Water Resources Research Institute. UNC-WRRI-82-171.

Overcash MR, Weber JB, Tucker W. 1986. Toxic and priority organics in municipal sludge land treatment systems. Cincinnati OH: U.S. Environmental Protection Agency, Office of Research and Development. EPA/600/2-86/010. NTIS No. PB86-150208.

Overturf ML, Druilhet RE, Liehr JG, et al. 1979. Phthalate esters in normal and pathological human kidneys. Bull Environ Contam Toxicol 22:536-542.

8. REFERENCES

Packham RF, Beresford SA, Fielding M. 1981. Health related studies of organic compounds in relation to re-use in the United Kingdom. Sci Total Environ 18:167-186.

Pancorbo OC, Varney TC. 1986. Fate of synthetic organic chemicals in soil-groundwater systems. Vet Hum Toxicol 28:127-143.

* Pankow JF, Ligocki MP, Rosen ME, et al. 1988. Adsorption/thermal desorption with small cartridges for the determination of trace aqueous semivolatile organic compounds. Anal Chem 60:40-47.

* Perwak J, Goyer M, Schimke G, et al. 1981. An exposure and risk assessment for phthalate esters: Di(2-ethylhexyl) phthalate, di-n-butyl phthalate, dimethyl phthalate, diethyl phthalate, di-n-octyl phthalate, butyl benzyl phthalate. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA-440/4-81-020. NTIS No. PB85-211936.

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

PHRED. 1988. Public Health Risk Evaluation Database. U.S. Environmental Protection Agency, Washington, DC. March 1988.

Pizzoli M, Scandola M, Ceccorulli G, et al. 1985. Rate of absorption of di-n-butyl phthalate in glassy poly(vinylchloride). Polym Comm 26:107-109.

* Popp JA, Marsman DS, Cattley RC, et al. 1989. Hepatocarcinogenicity and peroxisome proliferation. CIIT Activities 9:1-7.

Rao MS, Reddy JK. 1987. Peroxisome proliferation and hepatocarcinogenesis. Carcinogenesis 8:631-636.

* Ray LE, Murray HE, Giam CS. 1983. Organic pollutants in marine samples from Portland, Maine. Chemosphere 12:1031-1038.

Reddy JK, Rao MS, Lalwani ND, et al. 1987. Induction of hepatic peroxisome proliferation by xenobiotics. In: Fahimi HD, Sies H, eds. Peroxisomes in biology and medicine. Heidelberg, West Germany: Springer-Verlag, 255-262.

* Reel JR, Lawton AD, Lamb TC. 1984. Di(n-butyl) phthalate: Reproduction and fertility assessment in CD-1 mice when administered in the feed. Research Triangle Park, NC: National Institute of Environmental Health Science, National Toxicology Program. NTP 84-411. NTIS No. PB85-144798.

8. REFERENCES

Rowland IR, Cottrell RC, Phillips JC. 1977. Hydrolysis of phthalate esters by the gastro-intestinal contents of the rat. Food Cosmet Toxicol 15:17-21.

* Rubin RJ, Kozumbo W, Kroll R. 1979. Ames mutagenic assay of a series of phthalic acid esters: Positive response of the dimethyl and diethyl esters in TA 100 [Abstract]. Toxicol Appl Pharmacol 48:A133.

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

Saido K, Motohashi S, Kuroki T. 1980. Studies on the thermal decomposition of phthalic acid esters. Thermal decomposition of di-n-butyl phthalate and analysis of its decomposed products. Nihon Daigaku Yakugaku Kenkyu Hokoku 20:1-10.

Salthouse TN, Matlaga BF, O'Leary RK. 1973. Microspectrophotometry of macrophage lysosomal enzyme activity: A measure of polymer implant tissue toxicity. Toxicol Appl Pharmacol 25:201-211.

* Sanders HO, Mayer FL, Jr, Walsh DF. 1973. Toxicity, residue dynamics, and reproduction effects of phthalate esters in aquatic invertebrates. Environ Res 6:84-90.

Sandmeyer EE. Kirwin CJ Jr. 1981. Esters. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. 3rd ed. Volume 2A: Toxicology. New York, NY: John Wiley and Sons, 2344-2412.

* Sax NI, Lewis RJ Sr, eds. 1987. Hawley's condensed chemical dictionary. 11th ed. New York, NY: Van Nostrand Reinhold Company, 372.

* Schulsinger C, Mollgaard K. 1980. Polyvinly chloride dermatitis not caused by phthalates. Contact Dermatitis 6:477-480.

* Scott RC, Dugard PH, Ramsey JD, et al. 1987. In vitro absorption of some o-phthalate diesters through human and rat skin. Environ Health Perspect 74:223-227.

Scott RC, Dugard PH, Ramsey JD, et al. 1989. Errata Env Hlth Perspect 79:323.

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

Seth PK. 1982. Hepatic effects of phthalate esters. Environ Health Perspect 45:27-34.

8. REFERENCES

Shibata K, Motooka K, Murata K, et al. 1982. Increase in growth rate and activity of the trytophan-NAD pathway caused by di-n-butyl phthalate in rats fed on a tryptophan-limited diet. J Nutr Sci Vitaminol 28:173-177.

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

* Shahin MM, Von Borstel RC. 1977. Mutagenic and lethal effects of alpha-benzene hexachloride, dibutyl phthalate and trichloroethylene in Saccharomyces cerevisiae. Mutat Res 48:173-180.

Shanker R, Ramakrishna C, Seth PK. 1985. Degradation of some phthalic acid esters in soil. Environ Pollut (Series A) 39:1-7.

* Shea PJ, Weber JB, Overcash MR. 1982. Uptake and phytotoxicity of di-n-butyl phthalate in corn (Zea mays). Bull Environ Contam Toxicol 29:153-158.

* Sheldon LS, Hites RA. 1979. Sources and movement of organic chemicals in the Delaware River. Environ Sci Technol 13:574-579.

Shibko SI, Blumenthal H. 1973. Toxicology of phthalic acid esters used in food-packaging material. Env Hlth Perspect 3:131-137.

* Shiota K, Nishimura H. 1982. Teratogenicity of di(2-ethylhexyl) phthalate (DEHP) and di-n-butyl phthalate (DBP) in mice. Environ Health Perspect 45:65-70.

* Shiota K, Chou MJ, Nishimura H. 1980. Embryotoxic effects of di-2-ethylhexyl phthalate (DEHP) and di-n-butyl phthalate (DBP) in mice. Environ Res 22:245-253.

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

Singh AR, Lawrence WH, Autian J. 1973. Embryonic-fetal toxicity and teratogenic effects of adipic acid esters in rats. J Pharm Sci 62:1596-1600.

Sittig M. 1985. Handbook of toxic and hazardous chemicals and carcinogens. 2nd ed. Park Ridge, NJ: Noyes Publications, 311-312.

* Smith CC. 1953. Toxicity of butyl stearate, dibutyl sebacate, dibutyl phthalate, and methoxyethyl oleate. AMA Arch Ind Hyg Occup Med 7:310-318.

8. REFERENCES

* Smith RM. 1988. Supercritical fluid chromatography. Anal Chem 60:1394A.

SRI. 1985. Directory of chemical producers: United States of America. Menlo Park, CA: SRI International, 799.

SRI. 1986. Directory of chemical producers: United States of America. Menlo Park, CA: SRI International, 9055.

SRI. 1987. Directory of chemical producers: United States of America. Menlo Park, CA: SRI International, 889.

* SRI. 1988. Directory of chemical producers: United States of America. Menlo Park, CA: SRI International, 870.

* Stalling DL, Hogan JW, Johnson JL. 1973. Phthalate ester residues-Their metabolism and analysis in fish. Environ Health Perspect 3:159-173.

* Stanley JS. 1986. Broad scan analysis of the FY82 national human adipose tissue survey specimens: Volume I-Executive summary. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA 560/5-86-035.

Steen WC, Paris DF, Baughman GL. 1980. Effects of sediment sorption on microbial degradation of toxic substances. Contaminants and Sediments 1:477-482.

Streufert JM, Jones JR, Sanders HO. 1980. Toxicity and biological effects of phthalate esters on midges (Chironomus plumosus). Trans Mo Acad Sci 14:33-40.

Stott WT. 1988. Chemically induced proliferation of peroxisomes: Implications for risk assessment. Regul Toxicol Pharmacol 8:125-159.

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

* Sullivan KF, Atlas EL, Giam CS. 1982. Adsorption of phthalic acid esters from seawater. Environ Sci Technol 16:428-432.

* Swartz RC, Schults DW, Ditsworth GR, et al. 1983. Sediment toxicity, contamination, and macrobenthic communities near a large sewage outfall. In: Boyle TP, ed. Validation and predictability of laboratory methods for assessing the fate and effects of contaminants in aquatic ecosystems. Philadelphia, PA: ASTM, 152-175.

8. REFERENCES

Tabak HH, Quave SA, Mashni CI, et al. 1981. Biodegradability studies with organic priority pollutant compounds. J. Water Pollut Control Fed 53:1503-1518.

Tagatz ME, Plaia GR, Deans CH. 1986. Toxicity of dibutyl phthalate-contaminated sediment to laboratory- and field-colonized estuarine benthic communities. Bull Environ Contam Toxicol 37:141-150.

* Takahashi T, Tanaka A. 1989. Biochemical studies on phthalic esters. V. Comparative studies on in vitro hydrolysis of di-n-butyl phthalate isomers in rats. Arch Toxicol 63:72-74.

* Tanaka A, Matsumoto A, Yamaha T. 1978. Biochemical studies on phthalic esters. III. Metabolism of dibutyl phthalate (DBP) in animals. Toxicology 9:109-123.

* Tanino M, Ikemoto I, Tanaka A. 1987. Enzyme levels in rat testis damaged experimentally with dibutyl phthalate. Jikeikai Med J 34:245-252.

Tavares IA, Vine ND. 1985. Phthalic acid esters inhibit arachidonate metabolism by rat peritoneal leucocytes. J Pharm Pharmacol 37:67-68.

Tavares IA, Bennett A, Gaffen JD, et al. 1984. The biological activities of phthalate esters on rat gastric muscle. Eur J Pharmacol 106:449-452.

* Taylor BF, Curry RW, Corcoran EF. 1981. Potential for biodegradation of phthalic acid esters in marine regions. Appl Environ Microbiol 42:590-595.

Thomas JA, Wienckowski DB, Gillies BA, et al. 1986. Effects of phthalic acid esters (PAEs) on the neonate and aspects of teratogenic actions. Environ Health Perspect 65:243-248.

* Thuren A. 1986. Determination of phthalates in aquatic environments. Bull Environ Contam Toxicol 36:33-40.

Timofievskaya LA, Balynina ES. 1979. [Neurotoxic action of some o-phthalic acid esters.] Toksikol Nov Prom Khim Veshchestv 15:123-128. (Russian)

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 8:317-320.

8. REFERENCES

* USITC. 1987. Synthetic organic chemicals - United States production and sales, 1986. Washington, DC: U.S. International Trade Commission. USITC Pub. No. 2009.

* USITC. 1988. Synthetic organic chemicals - United States production and sales, 1987. Washington, DC: U.S. International Trade Commission. USITC Pub. No. 2118.

* Verschueren K. 1983. Handbook of environmental data on organic chemicals. 2nd ed. New York, NY: Van Nostrand Reinhold Company, 468-471.

Vicedo JL, Pellin M, Vilanova E. 1985. Phthalates and organophosphorus compounds as cholinesterase inhibitors in fractions of industrial hexane impurities. Arch Toxicol 57:46-52.

* VIEW Database. 1989. Agency for Toxic Substances and Disease Registry (ATSDR), Office of External Affairs, Exposure and Disease Registry Branch, Atlanta, GA. June 20, 1989. (Map based on VIEW Database, June 12, 1989).

Virgin HI. 1988. Accumulation of di-n-butyl phthalate in plants and its effect on pigment and protein content. Physiologia Plantarum 72:190-196.

* Walker WW. 1984. Development of a fate/toxicity screening test. Gulf Breeze, FL: U. S. Environmental Protection Agency, Office of Research and Development. EPA-600/4-84-074. NTIS No. PB84-246370.

Walseth F, Nilsen OG. 1981. Reversibility of the effects of dibutyl phthalate (DBP) on rat liver and lung microsomal enzyme activities and serum protein levels. Acta Pharmacol Toxicol 49(Part 1):90.

* Walseth F, Nilsen OG. 1984. Phthalate esters: II. Effects of inhaled dibutyl phthalate on cytochrome P-450 mediated metabolism in rat liver and lung. Arch Toxicol 55:132-136.

* Walseth F, Nilsen OG. 1986. Phthalate esters: Effects of orally administered dibutyl phthalate on cytochrome P-450 mediated metabolism in rat liver and lung. Acta Pharmacol Toxicol 59:263-269.

* Walters SM. 1986. Cleanup of samples. In: Zweig G, Sherma J, eds. Analytical methods for pesticides and plant growth regulators. Vol 15. Principles, statistics, and applications. New York, NY: Academic Press, Inc., 67-110.

* Weast RC, ed. 1985. CRC handbook of chemistry and physics. Boca Raton, FL: CRC Press Inc., C-430.

8. REFERENCES

White RD, Carter DE, Earnest D, et al. 1980. Absorption and metabolism of three phthalate diesters by the rat small intestine. Food Cosmet Toxicol 18:383-386.

* White RD, Earnest DL, Carter DE. 1983. The effect of intestinal esterase inhibition on the in vivo absorption and toxicity of di-n-butyl phthalate. Food Chem Toxicol 21:99-101.

* Wieboldt RC, Adams GE, Later DW. 1988. Sensitivity improvement in infrared detection for supercritical fluid chromatography. Anal Chem 60:2422-2427.

Wilbourn J. Montesano R. 1982. An overview of phthalate ester carcinogenicity testing results: The past. Environ Health Perspect 45:127-128.

* Williams DT. 1973. Dibutyl- and di- (2-ethylhexyl) phthalate in fish. J Agric Food Chem 21:1128-1129.

* Williams DT, Blanchfield BJ. 1975. The retention, distribution, excretion and metabolism of dibutyl phthalate-7-^{14}C in the rat. J Agric Food Chem 23:854-858.

* Windholz M, Budavari S, eds. 1983. The Merck index: An encyclopedia of chemicals, drugs, and biologicals. 10th ed. Rahway, NJ: Merck and Company, Inc., 219.

* Wofford HW, Wilsey CD, Neff GS, et al. 1981. Bioaccumulation and metabolism of phthalate esters by oysters, brown shrimp, and sheepshead minnows. Ecotoxicol Environ Safety 5:202-210.

Wolfe NL, Paris DF, Steen WC, et al. 1980a. Correlation of microbial degradation rates with chemical structure. Environ Sci Technol 14:1143-1146.

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

Yanagita T, Enomoto N, Kuzuhara S. 1986. Effects of phthalate esters on liver lysosomal acid lipase and acid esterase in Vitro. Agric Biolog Chem 50:1653-1654.

Young LY, O'Connor O, Rivera MD. 1986. Toxic organic chemicals in waste streams: Anaerobic bioconversion to methane. Washington, DC: U.S. Department of Energy. DOE/CE/40657-1.

8. REFERENCES

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

* Zeiger E, Haworth S, Mortelmans K, et al. 1985. Mutagenicity testing of di (2-ethylhexyl) phthalate and related chemicals in Salmonella. Environ Mutagen 7:213-232.

* Zlatkis A, Kim K. 1976. Column elution and concentration of volatile compounds in biological fluids. J Chromatogr 126:475-485.

9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (K_d) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same time period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study or group of studies which produces significant increases in incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling value (CL) -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

9. GLOSSARY

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

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

Lethal Concentration($_{50}$) (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose($_{LO}$) (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

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

Lethal Time($_{50}$) (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study or group of studies which 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.

9. GLOSSARY

Minimal Risk Level (MRL) -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) 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 a chemical.

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

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

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

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ 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 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

9. GLOSSARY

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 humans, (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

PEER REVIEW

A peer review panel was assembled for di-n-butyl phthalate. The panel consisted of the following members: Dr. Theodore Kneip, Director, Laboratory of Environmental Studies, New York University Medical Center, Tuxedo, NY; Dr. Mildred Christian, President, Argus Research Laboratories, Inc., Horsham, PA; Dr. Sanford Bigelow, President, Multisciences, Inc., Kensington, MD; Dr. Gail Charnley, Private Consultant, Alexandria, VA; and Dr. Joseph P. Gould, Research Scientist, School of Civil Engineering, Georgia Institute of Technology, Atlanta, GA. These experts collectively have knowledge of di-n-butyl phthalate's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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

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