TOXICOLOGICAL PROFILE FOR DI-*n*-BUTYL PHTHALATE

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

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DISCLAIMER

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

UPDATE STATEMENT

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

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

FOREWORD

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

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

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

Each profile includes the following:

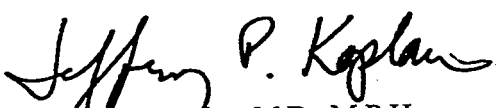
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

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

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

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

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



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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepared toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by *type of health effect* (death, systemic, immunologic, reproductive), by *route of exposure*, and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (404) 498-0057
E-mail: atsdric@cdc.gov ***Internet:*** http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity;* and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

*The National Institute of Environmental Health Sciences (*NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

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

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

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

1. William J. Adams, Ph.D., Kennecott Utah Copper Corporation, Magna, Utah;

2. Martin Alexander, Ph.D., Cornell University, Ithaca, New York;

3. C. Clifford Conaway, Ph.D., American Health Foundation, Valhalla, New York; and

4. Robert Rubin, Ph.D., Environmental Health Sciences, John Hopkins School of Public Health, Baltimore, Maryland

These experts 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. These 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.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about di-*n*-butyl phthalate and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Di-*n*-butyl phthalate has been found in at least 471 of the 1,585 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which di-*n*-butyl phthalate is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

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

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

1.1 WHAT IS DI-*n*-BUTYL PHTHALATE?

Di-*n*-butyl phthalate is an odorless and colorless or faintly yellow oily liquid that does not occur in nature. It is a chemical that is added to hard plastics to make them soft. The plastics that di-*n*-butyl phthalate is used most in are called polyvinyl chloride plastics and nitrocellulose lacquers. These plastics are used to make many products that we use every day such as carpets, paints, glue, insect repellents, hair spray, nail polish, and rocket fuel. In 1994, more than 17 million pounds (i.e., 7.8 million kilograms) of di-*n*-butyl phthalate were made.

Further information on the properties and uses of di-*n*-butyl phthalate can be found in Chapters 4 and 5.

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

Di-*n*-butyl phthalate enters the environment in many ways. Di-*n*-butyl phthalate is in many items made of plastics such as carpets, paint, and nail polish. When paint dries or new carpets are installed, a small amount of di-*n*-butyl phthalate enters the air. Di-*n*-butyl phthalate also gets into air by sticking to dust particles. In air, di-*n*-butyl phthalate usually breaks down within a few days, but not if it is stuck to dust. When it is on dust, di-*n*-butyl phthalate can move with the wind for many miles before dust drops to the ground. Di-*n*-butyl phthalate can get into soil when people throw out certain plastic items containing di-*n*-butyl phthalate and they get buried. In water and soil, bacteria break down di-*n*-butyl phthalate. This may happen in a day, or may take up to a month. How long it takes to break down di-*n*-butyl phthalate in soil or water depends on many factors. These factors include the outside temperature, because di-*n*-butyl phthalate breaks down more slowly when it is cold than when it is hot. If di-*n*-butyl phthalate does not break down in soil, it can get into groundwater and contaminate wells.

Further information on the uses of di-*n*-butyl phthalate and how it behaves in the environment can be found in Chapters 5 and 6.

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

Because di-*n*-butyl phthalate has so many uses, it is widespread in the environment. Most people are probably exposed to low levels in air. Some people may also be exposed to di-*n*-butyl phthalate in water, food, or both. Most of the time, the largest source of exposure is from air that contains di-*n*-butyl phthalate. Low levels (0.01 parts per billion [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 temporarily inside homes and offices, especially when products containing di-*n*-butyl phthalate, such as nail polish, are used or when new carpet containing di-*n*-butyl phthalate is installed.

Di-*n*-butyl phthalate is present in some drinking water supplies, usually at levels of around 0.1 to 0.2 ppb.

Another way you can be exposed is by eating food containing di-*n*-butyl phthalate. Some di-*n*-butyl phthalate in food comes from the materials used to package and store the food. Some comes from di-*n*-butyl phthalate taken up by fish and shellfish. Levels of di-*n*-butyl phthalate in food have been found to range from about 40 to 570 ppb.

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. You can read about this in Section 1.5. If you were exposed to high 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 in 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 released into the air, water, and soil is also of concern near garbage dumps and landfills. This is because large amounts of products that have di-*n*-butyl phthalate in them are thrown away at these sites, and the di-*n*-butyl phthalate can slowly come out of these 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 6.

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

If you eat or drink food or water containing di-*n*-butyl phthalate, 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 will enter your body through the lungs, but this has not been studied in detail. Di-*n*-butyl phthalate can also enter the body through the 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 3.

1.5 HOW CAN DI-*n*-BUTYL PHTHALATE AFFECT MY HEALTH?

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

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

Di-*n*-butyl phthalate appears to have relatively low toxicity, and large amounts are needed to cause injury. 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. 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. The levels of di-*n*-butyl phthalate that 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. Exposure to high levels of di-*n*-butyl phthalate might cause similar effects in humans as in animals, but this is not known. In animals, large amounts of di-*n*-butyl phthalate repeatedly applied to the skin for a long time cause mild irritation. Although the available data do not indicate that di-*n*-butyl phthalate causes cancer, this needs to be more thoroughly studied.

Additional information on the levels of exposure associated with harmful effects of di-*n*-butyl phthalate can be found in Chapters 2 and 3.

1.6 HOW CAN DI-*n*-BUTYL PHTHALATE AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

Very few studies have looked at how di-*n*-butyl phthalate can affect the health of children. It is likely that the health effects seen in children exposed to di-*n*-butyl phthalate will be similar to the effects seen in adults. We do not know whether children differ from adults in their susceptibility to di-*n*-butyl phthalate.

We do not know if exposure to di-*n*-butyl phthalate will result in birth defects or other developmental effects in people. Birth defects have been observed in animals exposed to high levels of di-*n*-butyl phthalate during development. The developing animal is sensitive to di-*n*-butyl phthalate. Death, low body weights, skeletal deformities, cleft palate, and damage to the testes have been observed in the offspring of animals ingesting large amounts of di-*n*-butyl phthalate.

We have no information to suggest that there are any differences between children and adults in terms of how much di-*n*-butyl phthalate will enter the body, where di-*n*-butyl phthalate can be found in the body, and how fast di-*n*-butyl phthalate will leave the body. We do not know if di-*n*-butyl phthalate can be transferred from the mother to an infant in breast milk or whether it can cross the placenta.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO DI-*n*-BUTYL PHTHALATE?

If your doctor finds that you have been exposed to significant amounts of di-*n*-butyl phthalate, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

Di-*n*-butyl phthalate is used in many products that are made from plastic. It is also in products like white glues and carpenter's glues made from a plastic known as polyvinyl acetate emulsion. Di-*n*-butyl phthalate is also used in some paints, furniture lacquer, and nail polish. When it is in anything, di-*n*-butyl phthalate is at a higher level when that product is new. There is less in products that are old. Because di-*n*-butyl phthalate may be in some toys, there is a concern that children chewing on such toys might be exposed. No measurements have yet been made to show whether children are exposed in this way.

1.8 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 breakdown products of di-*n*-butyl phthalate can be measured in urine. However, there is not enough information at this time 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 3 and 7.

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

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

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

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

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. EPA 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. NIOSH has established a limit of 5 milligrams per cubic meter (5 mg/m^3) di-*n*-butyl phthalate in workplace air to protect the health of workers.

Additional information on governmental regulations regarding di-*n*-butyl phthalate can be found in Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

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

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

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)
Fax: (404) 498-0057

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

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 605-6000

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO DI-*n*-BUTYL PHTHALATE IN THE UNITED STATES

Di-*n*-butyl phthalate is a colorless to faint yellow oily liquid that is not found naturally in the environment. It has a slightly ester smell and a strong, bitter taste. It has moderately low solubility in water, but is quite soluble in organic solvents such as alcohol, ether, benzene, and acetone. Di-*n*-butyl phthalate is used in plastics to make them more flexible, and is found in a number of consumer products, including home furnishings, paints, clothing, and cosmetic products. More than 8,500 tons (17 million pounds) of di-*n*-butyl phthalate was produced in the United States in 1994 by a number of companies in various locations.

Di-*n*-butyl phthalate is released to the environment during its production and use, with the vast majority being released to underground injection wells. Di-*n*-butyl phthalate is not expected to volatilize significantly from water to the atmosphere. In soils, migration to groundwater occurs, but is thought to be limited to sites with low organic content. The half-life of di-*n*-butyl phthalate vapor in air is calculated to be 14 daylight hours; in water and soils, >50% of di-*n*-butyl phthalate is degraded within 1–28 days.

The general population may be exposed to di-*n*-butyl phthalate from the air, water, and some foods. Air is probably the main source of di-*n*-butyl phthalate exposure for the general population, but some exposure may come from dairy products, fish, and seafood. Occupational exposures can occur through skin contact and by inhalation of vapors and dust. It is not known if exposure of children to di-*n*-butyl phthalate differs from that of adults. Di-*n*-butyl phthalate is present in some home furnishings, paints, vinyl flooring and floor wax; however, it is not known if children are more likely than adults to be exposed by increased contact with or proximity to these items. Children may also intentionally or unintentionally ingest soil, which may contain low levels of di-*n*-butyl phthalate.

The level of di-*n*-butyl phthalate exposure for the general population is expected to be in the low ppb range; in Canada, the estimated daily intake is 1.9–5.0 µg/kg body weight. Occupational exposure via inhalation has been estimated to be 143 µg/kg body weight/workday for workers employed in phthalate manufacturing.

Populations residing near hazardous waste disposal sites or municipal landfills may be subject to higher than average levels of di-*n*-butyl phthalate in ambient air or drinking water. No correlation of di-*n*-butyl phthalate fallout rates with specific sources or transport routes was found in a monitoring study in Sweden. However, di-*n*-butyl phthalate has been detected in leachate and groundwater near landfills and in groundwater near rapid infiltration beds where secondary sewage effluent was disposed of. Di-*n*-butyl phthalate has been identified in at least 471 of the 1,585 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL). However, the number of sites evaluated for di-*n*-butyl phthalate is not known.

2.2 SUMMARY OF HEALTH EFFECTS

The primary effects seen in animals following exposure to di-*n*-butyl phthalate are developmental and reproductive alterations. No data are available for developmental or reproductive effects in humans. Animal studies have shown that the development of the male reproductive system, especially the seminiferous epithelium of the testes, may be disrupted by *in utero* exposure to high doses of di-*n*-butyl phthalate during the critical period for reproductive development. Other developmental effects may also occur following *in utero* or perinatal exposure, and include increases in postimplantation losses, decreases in the number of live fetuses per litter, decreases in fetal and pup body weights, and increases in incidences of external, skeletal, and internal malformations. Reproductive effects are also seen in adult animals exposed to di-*n*-butyl phthalate. Fertility is reduced in male and female animals, and is related to testicular atrophy and seminiferous tubule damage in males; the mechanism in females is not known. Reproductive alterations may also extend to the offspring of exposed animals, and may include reduced fecundity and decreased sperm production. Minor liver, hematological, and renal effects, as well as changes in body weight, have also been observed in exposed rats.

Species differences in susceptibility to testicular damage have been noted. More severe testicular damage was seen in rats and guinea pigs than in mice and hamsters at the same dose level. This is thought to be due, at least in part, to differing levels of β-glucuronidase activity that may result in different levels of the free primary metabolite, mono-*n*-butyl phthalate, in the testes (see Section 3.5 Mechanisms of Action).

Developmental Effects. No human data are available for developmental effects of di-*n*-butyl phthalate. Animal studies have shown that acute- and intermediate-duration oral exposure to di-*n*-butyl phthalate causes a number of developmental effects, including increases in postimplantation losses, decreases in the number of live fetuses per litter, decreases in fetal/pup body weights, increases in

incidences of external, skeletal, and internal malformations, and altered reproductive development in the offspring. The lowest levels at which these effects were seen were varied widely. Decreases in the number of live pups/litter were seen following doses as low as 80 mg/kg/day in rats and 1,950 mg/kg/day in mice. Decreases in ano-genital distance, increases in undescended testes, and increases in abortions were seen at 500 mg/kg/day in rats, and increases in the incidence of external and skeletal malformations were seen at 750 mg/kg/day in rats. As discussed in Section 2.3, increased incidence of retained nipples and areolas (an anti-androgenic effect) in male rat pups exposed *in utero* is the basis for the acute-duration minimal risk level (MRL) for oral exposure. The lowest dose level resulting in disruption of androgen-regulated reproductive development in rats was 100 mg/kg/day. This is well above the levels expected to be encountered by the general population or at a well-regulated workplace.

Reproductive Effects. No human data are available for reproductive effects of di-*n*-butyl phthalate. Animal studies have shown that di-*n*-butyl phthalate affects fertility in both males and females. Decreases in fertility indices, reduced pregnancy rates, and shortened length of gestation have been seen in rodents exposed to di-*n*-butyl phthalate before or during gestation. Testicular atrophy has been observed in male rats, mice, and guinea pigs, but not hamsters, acutely exposed to di-*n*-butyl phthalate; however, rats are much more sensitive to the testicular effects than other animals examined (see Section 3.5 Mechanisms of Action).

Hepatic Effects. Mild liver effects have been seen in rats and mice orally exposed to di-*n*-butyl phthalate for acute or intermediate durations. These effects were increased liver weight, increased microsomal enzyme activity, inhibition of mitochondrial respiration, liver necrosis, and peroxisome proliferation. The lowest dose level at which effects were seen was 348 mg/kg/day.

Hematological Effects. Hematological effects have been observed in rats and mice exposed orally to high dose levels of di-*n*-butyl phthalate. These included anemia, decreased hematocrit, hemoglobin, and red blood cell levels.

Renal Effects. Renal effects of di-*n*-butyl phthalate were limited to decreased kidney weight in mice and increased kidney weight in rats exposed to high dose levels.

2.3 MINIMAL RISK LEVELS FOR DI-*n*-BUTYL PHTHALATE.

Inhalation MRLs

Information on the toxicity of inhaled di-*n*-butyl phthalate is sparse. Hypertension and hyperbilirubinemia were reported in workers exposed to 1.7–66 mg/m^3 di-*n*-butyl phthalate. Because the workers were exposed to other plasticizers, these effects cannot be definitively attributed to di-*n*-butyl phthalate exposure. Animal inhalation data are limited to a study that examined organ weight changes and hematological and serum chemistry parameters in rats exposed to di-*n*-butyl phthalate. Although organ weight (lung and brain) effects were observed, the toxicological significance of the alterations cannot be determined without histopathological examination of these tissues. In absence of reliable data, acute-, intermediate-, or chronic-duration inhalation MRLs were not derived.

Oral MRLs

- An MRL of 0.5 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to di-*n*-butyl phthalate.

The acute-duration oral MRL was based on a no-observed-adverse-effect level (NOAEL) of 50 mg/kg/day for developmental effects in the offspring of rats exposed to di-*n*-butyl phthalate on gestational days 12–21 and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). In this study, groups of 20 pregnant Sprague-Dawley rats (except 11 in the 500 mg/kg/day group) were treated with 0, 0.5, 5, 50, 100, or 500 mg/kg/day di-*n*-butyl phthalate by gavage in corn oil on gestational days 12–21. No developmental effects or clinical signs of toxicity were seen in pups exposed to 50 mg/kg/day or less *in utero*. The only treatment-related effect seen in the 100 mg/kg/day group was retained areolas and nipples in males (normally seen only in females) on postpartum day 14. This effect was dose-dependent, being more prominent at 500 mg/kg/day. Permanence of retained areolas and nipples was not assessed. Other statistically significant effects, seen only in males at 500 mg/kg/day level, were decreased ano-genital distance (12% decrease) and ano-genital distance/body weight at birth; smaller epididymides, dorsolateral prostate, and levator ani-bulbocavernosus muscle at sexual maturity; and decreased testes weight. Malformations of the male reproductive tract included absent or malformed epididymis, absent or malformed vas deferens, hypospadia, and unilaterally absent seminal vesicle. Histopathological lesions of the testis seen were seminiferous tubule degeneration, focal interstitial hyperplasia, and interstitial cell adenoma. In males, no significant changes were seen in age at preputial separation, or body, kidney, liver, adrenal, ventral

prostate, vas deferens, seminal vesicle, or other organ weights (other than those listed above). In female pups, no significant differences from controls were seen in age of onset of vaginal opening, body, liver, kidney, adrenal, ovary, or uterus weight, or gross morphology of the reproductive organs at sexual maturity.

Studies that have examined the acute toxicity of orally administered di-*n*-butyl phthalate have primarily focused on reproductive and developmental end points. Testicular atrophy, decreased testes weight, and decreased number of spermatocytes have been observed in rats, mice, and guinea pigs exposed to doses of 1,000 mg/kg/day and higher; a NOAEL of 500 mg/kg/day was identified. The developmental effects consisted of increases in post-implantation losses, decreases in fetal body weight, increases in external, skeletal, and internal malformations, and androgen-regulated developmental alterations (reduced ano-genital distance, increased number of retained nipples, decreased androgen-dependent tissue weights, delayed preputial separation). The smallest lowest-observed-adverse-effect level (LOAEL) for developmental toxicity was identified in a study in which increases in the incidence of retained areolas and nipples were observed in the offspring of rats exposed orally by gavage to $100 mg/kg/day di-*n*-butyl phthalate on gestational days 12–21. The NOAEL for this effect is 50 mg/kg/day. Although the systemic toxicity of di-*n*-butyl phthalate has not been adequately assessed following acute oral exposure, the results of intermediate-duration studies suggest that developmental toxicity would occur at similar or lower LOAELs than hepatic effects (the most sensitive systemic effect).

An intermediate-duration oral MRL was not derived for di-*n*-butyl phthalate. Systemic, reproductive, and developmental effects have been observed in animals. The liver appears to be the most sensitive systemic target in rats and mice exposed to di-*n*-butyl phthalate in the diet for 13 weeks. The hepatic effects consisted of cytoplasmic alterations suggestive of glycogen depletion, peroxisomal enzyme induction, decreased lipid deposition in the liver, decreased serum triglyceride and cholesterol levels, and inhibition of mitochondrial respiration. The reproductive effects consisted of testicular atrophy (including decreases in testes weight and degeneration of seminiferous tubule germinal epithelium) with decreases in spermatogenesis. Reproductive effects have been observed at 250 mg/kg/day and higher. Serious developmental effects have been observed in intermediate-duration studies. Decreases in fetal/pup survival, decreases in pup body weight, and impaired reproductive development in the male offspring (testicular degeneration and atrophy) have been observed. The lowest LOAEL for developmental toxicity is 80 mg/kg/day; decreases in fetal survival were observed at this dose.

The available intermediate-duration data suggest that developmental toxicity is the most sensitive toxic end point and should be used to derive an intermediate-duration MRL. The lowest LOAEL identified for

developmental toxicity is 80 mg/kg/day for decreases in the average number of pups per litter in rats exposed to dietary di-*n*-butyl phthalate in a continuous breeding study; a NOAEL was not identified. The 80 mg/kg/day is considered a serious LOAEL and is not appropriate for MRL derivation. Thus, an intermediate oral MRL was not derived for di-*n*-butyl phthalate.

No chronic-duration oral studies for humans or animals were identified; thus, a chronic oral MRL was not derived.

A chronic MRL for DNB was not derived. There were no adequate chronic-duration oral studies identified for humans or animals. EPA verified an RfD based on a study by Smith (1953). In this study, 10 rats were fed diets containing 0.01-1.25 % dibutyl phthalate. Half of the high dose group died within the first week of exposure. ATSDR did not have confidence in this study to derive an MRL due to the lack of detail and apparent conflict in the reported results. EPA also had low confidence in the study; the RfD received a low rating.

3. HEALTH EFFECTS

3.1 INTRODUCTION

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

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

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

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

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

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

3.2.1 Inhalation Exposure

3.2.1.1 Death

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

Studies in rats calculate acute inhalation LC_{50} values for rats of 25 g/m^3 (NTP 1995) and 4.25 g/m^3 (NTP 1995), and for mice of 25 g/m^3 (NTP 1995). No other studies regarding death in animals following inhalation exposure to di-*n*-butyl phthalate were located.

3.2.1.2 Systemic Effects

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

Respiratory Effects. No studies regarding respiratory effects in humans following inhalation exposure to di-*n*-butyl phthalate were located.

Information on the potential of di-*n*-butyl phthalate to induce respiratory effects is limited to a study by Kawano (1980a), which found an increase in relative lung weight in rats exposed to 50 mg/m^3 di-*n*-butyl phthalate 6 hours/day for 6 months (Kawano 1980a); lung weight was not altered in the 0.5 mg/m^3 group. The toxicological significance of the altered lung weight is difficult to assess in the absence of a study that examined histopathology.

Walseth and Nilsen (1984) reported a decrease in lung cytochrome P450 in rats exposed to 28.4 or 79.5 mg/m^3 but not 5.7 mg/m^3, di-*n*-butyl phthalate for 5 of 6 consecutive days, although no statistical significance was indicated.

Cardiovascular Effects. There is a limited amount of information available on the cardiovascular toxicity of di-*n*-butyl phthalate in humans. Hypertension was reported in workers exposed to di-*n*-butyl phthalate for 0.5–19 years at concentrations of 1.7–66 mg/m^3; the frequency 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.

Hematological Effects. No studies regarding hematological effects in humans following inhalation exposure to di-*n*-butyl phthalate were located.

No alterations in hematocrit, hemoglobin, or erythrocyte levels were observed in rats exposed to 50 mg/m^3 di-*n*-butyl phthalate 6 hours/day for 6 months (Kawano 1980a).

Hepatic Effects. Data on the hepatotoxicity of di-*n*-butyl phthalate is limited to a report of hyperbilirubinemia among workers exposed to 1.7–66 mg/m^3 for 0.5–19 years; the frequency 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.

Relative liver weight was not affected in rats exposed to 50 mg/m^3 di-*n*-butyl phthalate mist 6 hours/day for 6 months (Kawano 1980a). Small fluctuations in several serum chemistry parameters (serum enzymes, urea nitrogen, cholesterol) were noted in this study, but these were not clearly dose- or time-dependent.

Renal Effects. No studies regarding renal effects in humans following inhalation exposure to di-*n*-butyl phthalate were located.

Relative kidney weight did not differ from controls in rats exposed to 50 mg/m^3 di-*n*-butyl phthalate 6 hours/day for 6 months (Kawano 1980a).

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

Body Weight Effects. No studies regarding body weight effects in humans following inhalation exposure to di-*n*-butyl phthalate were located.

An approximate 13% decrease in body weight gain was observed in rats exposed to 50 mg/m^3 di-*n*-butyl phthalate 6 hours/day for 6 months (Kawano 1980a).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies regarding immunological effects in humans following inhalation exposure to di-*n*-butyl phthalate were located. Small fluctuations in white cell counts and percent neutrophils were found in rats exposed to 0.5 and 50 mg/m^3 di-*n*-butyl phthalate 6 hours per day for 6 months, but the changes were not dose- or time-dependent (Kawano 1980a), and do not appear to be clinically significant.

3.2.1.4 Neurological Effects

Workers exposed to di-*n*-butyl phthalate for 0.5–19 years at concentrations of 1.7–66 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 50 mg/m^3 di-*n*-butyl phthalate for 6 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 versus 1.47 g in controls).

3.2.1.5 Reproductive Effects

No studies regarding reproductive effects in humans following inhalation exposure to di-*n*-butyl phthalate were located. In rats, exposure to 0.5 or 50 mg/m^3 6 hours/day for 6 months caused no changes in relative testicular weight (Kawano 1980a).

3.2.1.6 Developmental Effects

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

3.2.1.7 Cancer

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

3.2.2 Oral Exposure

Table 3-1 and Figure 3-1 summarize the health effects observed following oral exposure of animals to di-*n*-butyl phthalate. These effects are discussed below.

3.2.2.1 Death

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

Di-*n*-butyl phthalate has low acute toxicity in animals. Single doses of 8,000 mg/kg killed four of nine 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; the cause of death was not determined. No deaths were observed at 125 mg/kg/day (Smith 1953). No deaths were reported in rats or mice that received up to 2,964 or 4,278 mg/kg/day, respectively, in the feed for 13 weeks (NTP 1995). However, pregnant rats may be more susceptible to the lethal effects of di-*n*-butyl phthalate, as 1–2 rats per treatment group died when exposed to 630 to 3000 mg/kg/day for 1 to 9 days during gestation (Ema et al. 1993, 1994; Saillenfait et al. 1998).

The highest NOAEL values and all reliable LOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.2 Systemic Effects

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

Table 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
	ACUTE EXPOSURE								
	Death								
1	Rat (Sprague-Dawley)	1 d (G)					8000	(4/9 died)	Smith 1953
2	Rat	1 d (G)					10000	(2/10 deaths)	White et al. 1983
3	Mouse	8 d 1x/d (G)					2500	(LD_{10})	Hardin et al. 1987
4	Mouse	Gd 6-13 1x/d (G)					2500	(5/49 deaths)	Hardin et al. 1987
	Systemic								
5	Rat (Sprague-Dawley)	Gd 12-21 1x/d (GO)	Hepatic	500 F					Mylchreest et al. 2000
			Renal	500 F					
			Endocr	500 F					
			Bd Wt	500 F					
6	Rat (Sprague-Dawley)	1 d (G)	Bd Wt	4000	8000	(unspecified decrease in body weight gain)			Smith 1953

Table 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)		Reference Chemical Form
	Reproductive							
7	Rat (Sprague-Dawley)	4 d 1x/d (G)		500		1000	(decreased testis weight)	Cater et al. 1977
8	Rat (Sprague-Dawley)	6 d 1x/d (G)				500	(decreased testis weight)	Cater et al. 1977
9	Rat (Wistar)	Gd 0-8 (GO)		1000		1250	(pregnancy rate decreased by 39%)	Ema et al. 2000a
10	Rat (Wistar)	7 d (G)				2400	(testicular atrophy)	Fukuoka et al. 1989
11	Rat (Wistar)	1 d (G)				2400	(testicular atrophy)	Fukuoka et al. 1990
12	Rat (Sprague-Dawley)	9 d 1x/d (GO)				2000	(severe testicular atrophy, decreased testes weight)	Gray et al. 1982
13	Rat (Sprague-Dawley)	Gd 12-21 1x/d (GO)		500 F				Mylchreest et al. 2000
14	Rat (Wistar)	7 d (F)				2100	(decrease in testicular weight and number of spermatocytes and spermatogonia)	Oishi and Hiraga 1980b

Table 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
15	Rat	7 d 1x/d (G)					2400	(histopathological damage, decreased testis weight)	Tanino et al. 1987
16	Mouse (TO)	9 d 1x/d (GO)			2000	(moderate testicular atrophy)			Gray et al. 1982
17	Gn Pig (Dunkin-Harley)	7 d 1x/d (GO)					2000	(severe testicular atrophy, decreased testes weight)	Gray et al. 1982
18	Hamster (Syrian)	9 d 1x/d (GO)		2000					Gray et al. 1982
	Developmental								
19	Rat (Wistar)	Gd 7-15 (GO)		500			630	(increased post implantation loss and decreased fetal body weights)	Ema et al. 1993
20	Rat (Wistar)	Gd 7-9 (GO)					750	(increased post implantation loss, decreased fetal body weights, skeletal malformations)	Ema et al. 1994
21	Rat (Wistar)	Gd 10-12 (GO)					750	(increased post implantation loss)	Ema et al. 1994

Table 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)		
22	Rat (Wistar)	Gd 13-15 (GO)				750	(increased post implantation loss; external and skeletal malformations)	Ema et al. 1994
23	Rat (Wistar)	Gd 7-9 (GO)				750	(increased implantation loss per litter, decreased number of live fetuses per litter, decreased fetal body weights, and increased skeletal malformations)	Ema et al. 1995a
24	Rat (Wistar)	Gd 10-12 (GO)				750	(increased implantation loss per litter, decreased number of live fetuses per litter, and decreased fetal body weights)	Ema et al. 1995a
25	Rat (Wistar)	Gd 13-15 (GO)				750	(skeletal and external malformations; increased percent postimplantation loss/litter)	Ema et al. 1995a
26	Rat (Wistar)	Gd 0-11 (F)				895	(complete resorption of litters)	Ema et al. 1997b
27	Rat (Wistar)	Gd 11-21 (F)		331		555	(increase in internal malformations)	Ema et al. 1998

Table 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
28	Rat (Wistar)	Gd 0-8 (GO)		250	500 (decreased fetal body weight)	750 (increased percent postimplantation loss/litter; decreased number of live fetuses/litter; altered sex ratios)	Ema et al. 2000a
29	Rat (Wistar)	Gd 12-14 1x/d (GO)				1000 M (decreased anogenital distance in fetuses)	Ema et al. 2000b
30	Rat (Wistar)	Gd 15-17 1x/d (GO)				500 M (increased incidence of undescended testes; decreased anogenital distance)	Ema et al. 2000b
31	Rat (Wistar)	Gd 18-20 1x/d (GO)				1000 M (decreased anogenital distance in fetuses; 12-15% decrease in fetal body weight)	Ema et al. 2000b
32	Rat (Sprague-Dawley)	Gd 14-Ld 3 1x/d (GO)				500 (reduced AGD, increased number of retained nipples, decreased androgen-dependent tissue weights in F1 males)	Gray et al. 1999

Table 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
33	Rat (Long- Evans)	Gd 16-19 1x/d (GO)				500 (reduced AGD, increased number of retained nipples, decreased androgen-dependent tissue weights in F1 males)	Gray et al. 1999
34	Rat (Sprague-Dawley)	Gd 12-21 1x/d (GO)			100 M (delayed preputial separation)	250 M (malformations of the epididymis; decreased AGD; retained nipples)	Mylchreest et al. 1999
35	Rat (Sprague-Dawley)	Gd 12-21 1x/d (GO)		50[b] M	100 M (retained areolas or nipples)	500 M (decreased anogenital distance; small sex accessory glands; decreased testes weight; malformations of reproductive tract)	Mylchreest et al. 2000
36	Rat (Sprague-Dawley)	Gd 14 (GO)		500	1000 (increased incidence of accessory 14th rib)	2000 (increased incidence of fused sternebrae and reproductive system anomalies; decreased percentage of male fetuses)	Saillenfait et al. 1998

Table 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
INTERMEDIATE EXPOSURE							
Systemic							
37	Rat (Wistar)	34-36 d (F)	Hepatic		470 (liver necrosis; decreased mitochondrial enzyme activities)		Murakami et al. 1986a
			Bd Wt		470 (15% decrease in body weight gain)		

Table 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
38	Rat (Fischer-344)	13 wk (F)	Resp	2964			NTP 1995
			Cardio	2964			
			Gastro	2964			
			Hemato	176	359 M (anemia)		
			Hepatic	176	359 (increased liver weight; increased palmitoyl-CoA oxidase activity)		
			Hepatic		176 (decreased serum triglyceride levels)		
			Renal	176	359 M (increased relative kidney weight)		
			Endocr	720	1540 M (decreased serum testosterone concentration)		
			Bd Wt	359	720 (8-11% decrease in body weight gain)	2964 (emaciation)	

Table 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less serious (mg/kg/day)		Serious (mg/kg/day)	
39	Rat (Wistar)	3 mo 1x/d (F)	Hemato	152	752 M	(decreasesd erythrocyte, hemoglobin, and hematocrit levels)		Schilling et al. 1992
			Hepatic	152	752	(decreased lipid deposition in liver and blood triglyceride levels; increased glucose and albumin levels)		
			Endocr	152	752	(decreased triidothyronine levels)		
40	Mouse (B6C3F1)	13 wk (F)	Resp	3689				NTP 1995
			Cardio	3689				
			Gastro	3689				
			Hemato	1601	3689	(decreased hematocrit)		
			Hepatic	812	1601	(cytoplasmic alterations)		
			Renal	3689				
			Endocr	3689				
			Bd Wt	353	812	(10% decrease in body weight gain)		

Table 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Neurological						
41	Rat (Wistar)	Daily 3 mo (F)		752			Schilling et al. 1992
	Reproductive						
42	Rat (Long- Evans)	weaning-Ld 20 1x/d (GO)			250 M (delayed preputial separation in the P0 generation)	500 (reduced fertility in P0 males and females; testicular atrophy, reduced sperm production in males; abortion in females)	Gray et al. 1999
43	Rat COBS CD	Daily 110 d (F)		500			IRDC 1984
44	Rat COBS CD	Daily 103 d (F)		500			IRDC 1984
45	Rat	34-36 d (F)		470		4700 (decreased testicular weight; marked spermatogenic damage)	Murakami et al. 1986a

Table 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
46	Rat (Fischer- 344)	Gd 1-21 (F)			950 F (shortening of gestation length)		NTP 1995
47	Rat (Fischer- 344)	13 wk (F)		359[c] M	720 M (degeneration of germinal epithelium in seminiferous tubules)	1540 M (hypospermia of the epididymis)	NTP 1995
				2943 F			
48	Rat (Sprague-Dawley)	26 wk (F)		256		509 (decreases in mating, pregnancy, and fertility indices)	NTP 1995
49	Rat (Wistar)	Daily 15 d (GO)				250 (testicular damage and defective spermatogenesis)	Srivastava et al. 1990
50	Mouse (B6C3F1)	13 wk (F)		3689[c] M			NTP 1995
				4278 F			
51	Mouse (Swiss CD-1)	18 wk (F)		580		1950 (decreases in fertility index)	NTP 1995
	Developmental						
52	Rat (Long- Evans)	weaning-Ld 20 1x/d (GO)				250 (malformations and reduced fecundity in F1 males and females)	Gray et al. 1999

Table 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
53	Rat COBS CD	103 d 1x/d (F)				500 (testicular degeneration in offspring)	IRDC 1984
54	Rat (Sprague-Dawley)	Daily Gd 3-21, Ld 2-20 (GO)				250 (degeneration and atrophy of seminferous tubules)	Mylchreest et al. 1998b
55	Rat (Fischer-344)	Gd1-21, Ld1-28, Pd28-56 (F)		120	240 (5% decrease in pup body weight) 480 M (hypospermia in offspring)	960 (decreased pup survival)	NTP 1995
56	Rat (Fischer-344)	Gd1-21, Ld1-28 (F)				950 (decreased number of pups/litter and pup body weight)	NTP 1995
57	Rat (Fischer-344)	Gd1-21, Ld1-28, 13 wk after weaning (F)		279		571 M (testicular atrophy)	NTP 1995

Table 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
58	Rat (Sprague-Dawley)	26 wk (F)		256		509 (decreased epididymal, cauda epididymal, testes, seminal vesicle, prostrate, and ovary wt, testicular degeneration and hypospermia)	NTP 1995
						80 (decreased number of live pups per litter)	
59	Mouse (B6C3F1)	Gd1-21, Ld1-28, Pd 28-56 (F)		920		1380 (decreased pup survival)	NTP 1995
				230	460 (decreased body weight after 4 weeks post weanling exposure)		

Table 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less serious (mg/kg/day)		Serious (mg/kg/day)		
60	Mouse (Swiss CD-1)	18 wk (F)		580			1950	(decreases in average number of litters per breeding pair and live pups per litter)	NTP 1995

[a]The number corresponds to entries in Figure 3-1.
[b]Used to derive an acute oral minimal risk level (MRL) of 0.5 mg/kg-day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = female; (G) = gavage; gastro = gastrointestinal; Gd = gestation day; (GO) = gavage in oil; Hemato = hematological; LD_{10}= lethal dose, 10% kill; Ld = lactation day; LOAEL = lowest-observed-adverse-effect level; M = male; mg/kg/day = milligram per kilogram per day; mo = month(s); NOAEL = no-observed-adverse-effect level; Pd = post-natal day; Resp = respiratory; wk = week(s); x = time

Figure 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral

Acute (≤14 days)

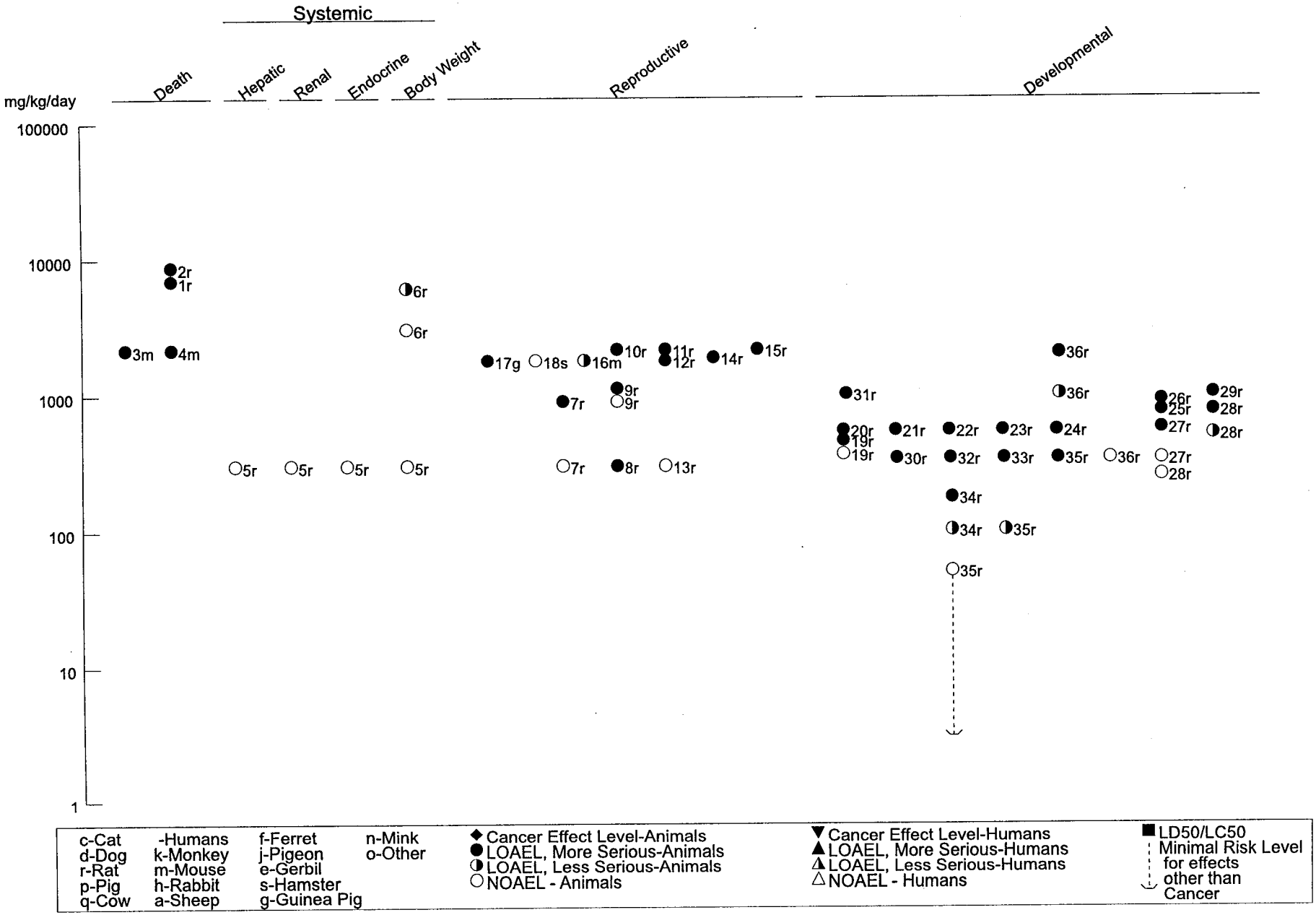
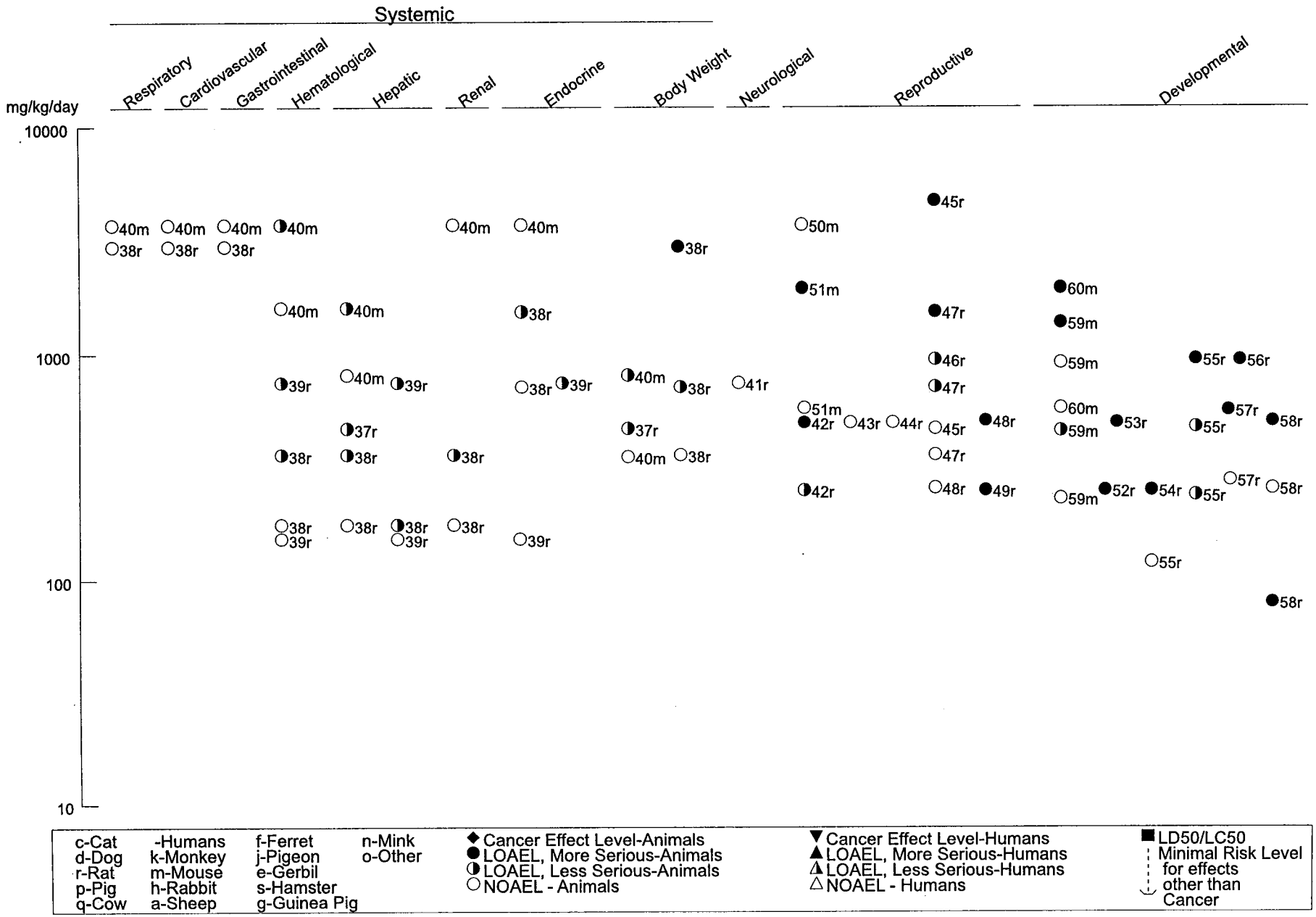


Figure 3-1. Levels of Significant Exposure to Di-*n*-butyl phthalate - Oral (*continued*)

Intermediate (15-364 days)



Respiratory Effects. No histological alterations were observed in the respiratory tract tissues of rats and mice exposed to up to 2,964 and 4,278 mg/kg/day, respectively, di-*n*-butyl phthalate in the diet for 13 weeks (NTP 1995).

Cardiovascular Effects. No histological alterations were observed in the heart of rats and mice exposed to up to 2,964 and 4,278 mg/kg/day, respectively, di-*n*-butyl phthalate in the diet for 13 weeks (NTP 1995).

Gastrointestinal Effects. No histological alterations were observed in the gastrointestinal tract tissues of rats and mice exposed to up to 2,964 and 4,278 mg/kg/day, respectively, di-*n*-butyl phthalate in the diet for 13 weeks (NTP 1995).

Hematological Effects. Minimally severe anemia was observed in male rats exposed to $369 mg/kg/day di-*n*-butyl phthalate in the diet for 13 weeks (NTP 1995). The study authors noted that hemoconcentration by dehydration (as evidenced by higher albumin concentrations) may have masked the effects, and that the anemia may have been more severe than the data indicated. No hematological effects were observed in the female rats. Decreases in erythrocyte, hemoglobin, and hematocrit levels were also observed in male rats exposed to 752 mg/kg/day in the diet (Schilling et al. 1992) and a decrease in hematocrit was observed in female mice exposed to 2,137 mg/kg/day di-*n*-butyl phthalate in the diet (NTP 1995).

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.

Musculoskeletal Effects. No studies regarding musculoskeletal effects in animals following oral exposure to di-*n*-butyl phthalate were located.

Hepatic Effects. In animals, minimal effects on the liver were 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 (1,000–2,600 mg/kg/day) for 7 days (Oishi and Hiraga 1980a, 1980b) or in rats and mice that received at least 359 or 2137 mg/kg/day, respectively, in the diet for 13 weeks (NTP 1995). Increased relative liver 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). 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). NTP (1995) reported hepatocellular cytoplasmic alterations, consistent with glycogen depletion, in rats and mice exposed to 720 and 1601 mg/kg/day, respectively, di-*n*-butyl phthalate in the diet for 13 weeks. Liver necrosis was noted at doses of 470 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; NTP 1995). No explanation for the discrepant results is evident.

Decreases in serum triglyceride and cholesterol levels were observed in rats exposed to dietary di-*n*-butyl phthalate for 13 weeks (NTP 1995). Although the mechanism for these alterations is not known, this finding may be associated with peroxisome proliferation.

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. In rats exposed for 13 weeks, induction of peroxisomal enzyme activity (acyl CoA oxidase) was

observed at doses of 353 mg/kg/day, but not 176 mg/kg/day (NTP 1995). 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). Relative kidney weights were increased in male and female rats administered 359 and 712 mg/kg/day, respectively, for 13 weeks, and absolute and relative kidney weights were increased in female mice exposed to 238 mg/kg/day for 13 weeks (NTP 1995); decreased absolute kidney weights in male and female rats and male mice were considered secondary to body weight changes. No histopathologic lesions of the kidney have been observed in rats exposed to di-*n*-butyl phthalate (BIBRA 1986; Nikonorow et al. 1973; NTP 1995).

Endocrine Effects. No histological alterations in endocrine tissue have been observed in rats and mice exposed to up to 2,964 and 4,278 mg/kg/day, respectively, di-*n*-butyl phthalate in the diet for 13 weeks (NTP 1995). Phthalates are a class of chemicals that have been implicated as having estrogenic properties. There is *in vitro* evidence of the weak estrogenic behavior of di-*n*-butyl phthalate; however, *in vivo* results do not support these findings. Studies in rats indicate that di-*n*-butyl phthalate has anti-androgenic properties (Ema et al. 1998, 2000b; Gray et al. 1999; Mylchreest et al. 1999, 2000). These are discussed in Section 3.6 Endocrine Disruption.

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

Ocular Effects. No studies regarding ocular effects in humans following oral exposure to di-*n*-butyl phthalate were located.

No changes to the refracting media of the eye were noted in Wistar rats receiving 1,075 (male) or 1,111 (female) mg/kg/day di-*n*-butyl phthalate in the feed for 3 months (Schilling et al. 1992).

Body Weight Effects. 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; NTP 1984, 1995; Oishi and Hiraga 1980a; Smith 1953). Decreases in body weight gain were only observed at higher doses (8,000 mg/kg/day) in the acute-duration studies (Gray et al. 1982; Smith 1953). Decreases in body weight gain have been observed at lower doses following repeated exposure: 250 mg/kg/day in rats exposed for 34–36 days (Murakami et al. 1986a), 720 mg/kg/day in rats for 13 weeks (NTP 1995), and 353 mg/kg/day in mice exposed for 13 weeks (NTP 1995).

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 3-1 and Figure 3-1.

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

3.2.2.3 Immunological and Lymphoreticular Effects

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

3.2.2.4 Neurological Effects

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

Male and female Wistar rats exposed to 1,075 and 1,111 mg/kg/day di-*n*-butyl phthalate, respectively, in the feed for 3 months showed no signs of neurological impairment, as assessed by a functional observational battery of sensory and motor function parameters (Schilling et al. 1992). No gross or histological lesions of the brain were noted in rats or mice exposed to up to 2,964 or 4,000 mg/kg/day, respectively, for 13 weeks, or exposed throughout gestation, lactation, and then for 13 weeks.

3.2.2.5 Reproductive Effects

A weak, negative correlation was reported between sperm density and di-*n*-butyl phthalate concentration in semen from male university students (Murature et al. 1987). However, lack of data and inadequate data analysis in this study prevent the establishment of a causal relationship between sperm density and di-n-butyl phthalate. No other studies regarding reproductive effects in humans following oral exposure to di-*n*-butyl phthalate were located.

Oral exposure to di-*n*-butyl phthalate had adverse effects on the male reproductive system in several animal species (rats, mice, and guinea pigs). Testicular atrophy (including decreases in testicular weight, decreases in spermatocytes and spermatogonia, and sloughing of germ cells) have been observed in Sprague-Dawley or Wistar rats receiving 1,000 mg/kg/day or higher for 4 or 5 days (Cater et al. 1977; Gray and Gangolli 1986), 2,400 mg/kg/day for 1 or 7 days via gavage (Fukuoka et al. 1989, 1990), or 2,100 mg/kg/day in the diet for 7 days (Oishi and Hiragi 1980b). Gray et al. (1999) found that Long-Evans hooded rats exposed to 250 mg/kg/day from weaning through puberty and young adulthood also showed testicular atrophy and reduced sperm production. Fukuoka et al. (1990) observed sloughing of the germ cells in the seminiferous tubules 6 hours after dosing with di-*n*-butyl phthalate. Three to seven days after a single gavage dose was administered, more severe damage including dissociation of mature germ cells (i.e., spermatozoa, spermatids, and spermatocytes) from seminiferous tubule germinal epithelium was observed (Fukuoka et al. 1990).

Srivastava et al. (1990) found a minimal amount of seminiferous tubular damage (approximately 5% of tubules affected) in Wistar rats following gavage administration of 250 mg/kg/day in groundnut oil for 15 days, more moderate tubular damage (20% affected) with decreased testicular weight at 500 mg/kg/day, and marked degeneration of seminiferous tubules at 1,000 mg/kg/day. Similarly, Gray et al. (1999) found testicular atrophy, with accompanying decreased sperm production, in Long-Evans rats following gavage administration of 500, but not 250 mg/kg/day, di-*n*-butyl phthalate in corn oil from weaning into adulthood; no histological data were provided. In contrast, NTP (1995) did not find testicular alterations in rats exposed to 359 mg/kg/day in the diet for 13 weeks. Testicular atrophy was observed at 720 mg/kg/day and hypospermia at 1,540 mg/kg/day. The different routes of exposure (gavage versus diet) may explain the different results in these studies.

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 2 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, active spermatogenesis was observed in almost all tubules. However, vacuolation of germinal epithelium and decreased number of sperm were still evident.

Species and sex differences in the reproductive toxicity of di-*n*-butyl phthalate are evident. While severe seminiferous tubular atrophy was observed in rats and guinea pigs at 2,000 mg/kg/day for 7–9 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). Testicular atrophy was observed in rats following intermediate-duration exposure to 720 mg/kg/day (NTP 1995); this effect was not observed in mice exposed to 3,689 mg/kg/day (NTP 1995). The species differences may be related to the greater ability of some species to conjugate the primary metabolite of di-*n*-butyl phthalate (see Section 3.3.3.2).

No histopathological alterations in reproductive tissues or effects on estrus cycling were observed in female rats following a 13-week exposure to doses as high as 2,943 mg/kg/day (NTP 1995), and no statistically significant differences from controls in number of implantation sites or live pups per litter were seen in Sprague-Dawley rats exposed to up to 500 mg/kg/day on gestational days 12–21 (Mylchreest et al. 2000). However, pregnancy rate (nonpregnancy=no detectable implantation sites) was decreased in female Wistar rats (bred to untreated males) receiving 1,250 or 1,500 mg/kg/day di-*n*-butyl phthalate via gavage administration on gestational days 0–8, and preimplantation losses were increased at 1,500 mg/kg/day (Ema et al. 2000a). Also, a cross-over mating study (NTP 1995) in mice suggests that di-*n*-butyl phthalate may impair fertility in exposed females. Decreases in fertility and average number of litters per breeding pair and live pups per litter were observed in female mice exposed to 1,950 mg/kg/day and mated with control males.

In a three-generation study in Long-Evans rats, exposure of the first generation (F_0) males to 250 mg/kg/day di-*n*-butyl phthalate via gavage administration from weaning through early adulthood statistically significantly delayed preputial separation (an index of puberty) in a dose-dependent manner (39.5, 42.6, 43.4, and 44.4 days in the 0, 250, 500, and 1,000 mg/kg/day groups, respectively) (Gray et al. 1999). In the same study, exposure to $500 mg/kg/day resulted in decreased fertility in (F_0) males and females (bred to untreated rats), and caused mid-gestation abortions in females bred to untreated males (Gray et al. 1999). Infertility in males was related to testicular atrophy and reduced sperm production.

Reproductive malformations in second generation (F_1) male pups (exposed to di-*n*-butyl phthalate only *in utero* and via lactation) included testicular nondescent and hypospadias. Reduced fecundity was seen in similarly treated (250 or 500 mg/kg/day) (F_1) mating pairs under continuous breeding conditions, which may have been caused, at least in part, by reduced cauda epididymal sperm counts in (F_1) males.

The highest NOAEL and all reliable LOAEL values for reproductive effects are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.6 Developmental Effects

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

A number of studies have examined the developmental toxicity of di-*n*-butyl phthalate in animals following acute- and intermediate-duration oral exposure (Ema et al. 1993, 1994, 1995a, 1997a, 1997b, 1998, 2000a, 2000b; Gray et al. 1999; Hardin 1987; IRDC 1984; Mylchreest et al. 1998b, 1999, 2000, NTP 1995; Saillenfait et al. 1998). The observed developmental effects include increases in postimplantation losses, decreases in the number of live fetuses per litter, decreases in fetal/pup body weights, increases in incidences of external, skeletal and internal malformations, and altered reproductive development in the offspring. A series of gavage-administration studies, conducted by Ema and associates, reported postimplantation losses and decreases in the number of live fetuses in Wistar rats receiving gavage doses of 630 mg/kg/day on gestational days 7–15 (Ema et al. 1993) or 750 mg/kg/day on gestational days 0–8 (Ema et al. 2000a), 7–9 (Ema et al. 1994, 1995a), 10–12 (Ema et al. 1994, 1995a), or 13–15 (Ema et al. 1994); no losses were reported after dosing with 500 mg/kg/day on gestational days 7–15 (Ema et al. 1993). In a series of single gavage dose studies by Ema et al. (1997a), postimplantation losses were observed in rats dosed with 1,500 mg/kg/day di-*n*-butyl phthalate on gestational days 6, 8, 9, 10, 12, 13, 14, 15, and 16. At doses of 750 mg/kg/day (administered on gestational days 7–15), >80% of the litters were totally resorbed; decreases in maternal body weight and food consumption were also observed at this dosage (Ema et al. 1993). Approximately 10–20% of the litters were completely resorbed when the dams were dosed with 750 mg/kg/day for 3 days during gestation (between gestational days 7 and 17) (Ema et al. 1994, 1995a); 20–100% were totally resorbed at 1,500 mg/kg/day (Ema et al. 1994, 2000b); no litters were totally resorbed following exposure to up to 1,500 mg/kg/day on gestational days 18–20 (Ema et al. 2000b). Maternal food consumption and body

weight gain were decreased at 500 mg/kg/day or greater (Ema et al., 2000b). Hardin et al. (1987) also reported fetal losses (no viable litters) in mice receiving gavage doses of 2,500 mg/kg/day on gestational days 6–13. A pilot study conducted by Saillenfait et al. (1998) also found postimplantation losses in Sprague-Dawley rats receiving single gavage doses of 2,000 mg/kg/day on gestational days 13, 14, or 15 (loss per litter of 23.04, 64.46, or 37.55%, respectively). Increased pup losses have also been observed in intermediate-duration studies. Female Long-Evans rats treated with 500 mg/kg/day di-*n*-butyl phthalate from weaning through puberty and gestation aborted their litters around mid-gestation (Gray et al. 1999). Rats exposed to 250 or 500 mg/kg/day di-*n*-butyl phthalate *in utero* and via lactation produced fewer pups than controls (means of 108, 78, and 59 pups/breeding pair over 11 breeding cycles for control, 250, and 500 mg/kg/day, respectively) when mated with similarly treated rats under continuous breeding conditions (Gray et al. 1999). A decrease in the number of live pups per litter was observed in rats exposed via the diet to 950 mg/kg/day on gestational days 1–21 (NTP 1995). Decreases in the number of live pups per litter were also observed in continuous breeding studies conducted for NTP (1995) in which rats and mice were exposed to 80 and 1,950 mg/kg/day, respectively, di-*n*-butyl phthalate in the diet for 112 or 98 days, respectively. A NOAEL for this effect was not identified in the rat study; the mouse study identified a NOAEL of 580 mg/kg/day. Another developmental toxicity study conducted for NTP (1995) reported decreased survival in the pups of rats and mice exposed to di-*n*-butyl phthalate in the diet throughout gestation, lactation, and postnatal days 28–56. The LOAELs identified in the rat and mouse studies were 960 and 1,380 mg/kg/day, respectively; the NOAELs for pup survival were 720 and 920 mg/kg/day, respectively.

Decreased body weights have been observed in the offspring of rats following acute- or intermediate-duration exposure (Ema et al. 1993, 1994, 1995a, 1997a, 2000a, 2000b; NTP 1995). Dose-related decreases in fetal body weights were observed in rats receiving gavage doses of 500 mg/kg/day or higher di-*n*-butyl phthalate on gestational days 0–8 (Ema et al. 2000a) or 630 mg/kg/day or higher on gestational days 7–15 (Ema et al. 1993). Decreases in body weights were also observed in the fetuses of rats receiving gavage doses of 750 mg/kg/day on gestational days 7–9, 10–12, or 13–15 (Ema et al. 1994, 1995a), 1,000 mg/kg/day on gestational days 12–14 or 18–20 (Ema et al. 2000b), or 1,500 mg/kg/day on gestational days 6, 7, 8, 9, 10, 11, 16, or 15–17 (Ema et al. 1997a, 2000b). Body weight was not affected when the dams were exposed on gestational days 12, 13, 14, or 15. Similarly, rat pups exposed *in utero* to up to 500 mg/kg/day on gestational days 12–21 had no significant decrease in body weight (Mylchreest et al. 2000). Several of the NTP (1995) developmental toxicity studies found decreases in pup body weight. The identified LOAELs were 240 mg/kg/day (NOAEL of 120 mg/kg/day) in rats exposed

throughout gestation, lactation, and postnatal days 28–56, 950 mg/kg/day in rats exposed throughout gestation and lactation, and in mice exposed to 460 mg/kg/day (NOAEL of 230 mg/kg/day) throughout gestation, lactation, and postnatal days 28–56.

External and skeletal malformations have been observed in the offspring of rats exposed to di-*n*-butyl phthalate for acute durations (Ema et al. 1993, 1994, 1995, 1997a; Saillenfait et al. 1998). Increases in the incidence of skeletal and/or external malformation have been observed in a number of gavage administration studies conducted by Ema and associates. The skeletal effects, primarily fusion or absence of cervical vertebral arches, were observed in the fetuses of rats exposed to 750 mg/kg/day on gestational days 7–9 or 13–15 (Ema et al. 1994, 1995a). External malformations (cleft palate) were observed in fetuses of rats receiving 750 mg/kg/day gavage doses of di-*n*-butyl phthalate on gestational days 13–15, but not on days 7–9 or 10–12 (Ema et al. 1994, 1995a). Saillenfait et al. (1998) also found increases in the occurrence of skeletal variations (accessory 14th rib) and malformations (fused sternebrae) in the fetuses of rats receiving a single gavage dose of 1,000 or 2,000 mg/kg/day, respectively, on gestational day 14. A serial study conducted by Ema et al. (1997a) was designed to identify the critical periods for skeletal and external malformations in rats receiving a single gavage dose of 1,500 mg/kg/day on one of gestational days 6–16; maternal toxicity (death or decreases in adjusted body weight gain) was not observed in this study. Increases in external malformations were only observed in the fetuses exposed on gestational day 15 and skeletal malformations were observed in fetuses exposed on gestational days 8, 9, or 15.

Acute- and intermediate-duration studies have reported reproductive effects in rat offspring (Ema et al. 1998, 2000a, 2000b; Gray et al. 1999; IRDC 1984; Mylchreest et al. 1998b, 1999, 2000; NTP 1995). Rats exposed to 500 mg/kg/day di-*n*-butyl phthalate on gestational days 12–21 exhibited a number of developmental reproductive abnormalities, including retained nipple buds or areolas, decreased anogenital distance and anogenital distance/body weight ratio, absent or malformed epididymis, absent or malformed vas deferens, and hypospadias (Mylchreest et al. 2000). Only retained nipple buds/areolas were seen in rats exposed to 100 mg/kg/day, and no developmental effects were seen at 50 mg/kg/day or less. This study was used to derive an acute-duration oral MRL for di-*n*-butyl phthalate. In an acute-duration study by Ema et al. (1998), an increased incidence of undescended testes (an internal malformation) and decreased anogenital distance and anogenital distance/body weight ratio were observed in the fetuses of rats receiving gavage doses of 555 or 661 mg/kg/day on gestational days 11–21; no effects were observed at 331 mg/kg/day. Effects seen in other acute-duration studies involving gestational or gestational/

lactational exposure to 250–1,500 mg/kg/day included retained nipple buds or areolas, decreased anogenital distance and anogenital distance/body weight ratio, absent or malformed epididymis, degeneration of seminiferous epithelium, absent or malformed vas deferens, decreased androgen-dependent tissue weights (ventral prostate, epididymis, cauda epididymis, testes, glans penis, and levator ani-bulbocavernosus), hypospadias, increased incidence of cryptorchidism, and delayed preputial separation (Ema et al. 2000a, 2000b; Gray et al. 1999; Mylchreest et al. 1999). The reproductive effects observed in the intermediate-duration studies are similar to those observed in adult rats orally exposed to di-*n*-butyl phthalate, including degeneration and atrophy of the seminiferous tubules and hypospermia. Degeneration and atrophy of the seminiferous tubules were observed in the offspring of rats receiving daily gavage doses of 250 mg/kg/day on gestational days 3–21 and lactational days 2–20 (Mylchreest et al. 1998b). Male offspring of rat dams exposed to 250 mg/kg/day di-*n*-butyl phthalate or higher from weaning through mating, gestation, and lactation showed reduced cauda epididymal sperm counts and increased incidence of urogenital malformations (Gray et al. 1999). Female offspring in the same study (Gray et al. 1999) showed increased incidence of uterine abnormalities (partial agenesis or lack of implants in one uterine horn). Two studies conducted for NTP (1995) and a study by IRDC (1984) examined reproductive organs of F_1 rats exposed to di-*n*-butyl phthalate *in utero*, during lactation, and for 7 (IRDC 1984), 10 (NTP 1995), or 13 weeks postweaning. IRDC (1984) and NTP (1995) reported testicular degeneration/atrophy in the F_1 rats exposed to 500 (IRDC 1984) or 571 (NTP 1995) mg/kg/day; this effect was not observed in offspring of rats only exposed *in utero* and during lactation (IRDC 1984). Decreases in epididymal, cauda epididymal, testes, seminal vesicle, prostate gland, and ovary weights, testicular degeneration, and hypospermia were observed in the F_1 rats exposed to 509 mg/kg/day *in utero*, during lactation, and through delivery of the F_2 generation (10 weeks) (NTP 1995).

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.7 Cancer

No studies regarding carcinogenic effects of di-*n*-butyl phthalate in humans after oral exposure to di-*n*-butyl phthalate were located. Rats exposed for 15–21 months to doses of 100–500 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.

3.2.3 Dermal Exposure

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

3.2.3.1 Death

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

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

3.2.3.2 Systemic Effects

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

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 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.

Table 3-2. Levels of Significant Exposure to Di-*n*-butyl phthalate - Dermal

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
				Less serious (mg/kg/day)		Serious (mg/kg/day)		
ACUTE EXPOSURE								
Systemic								
Rabbit	1x (F)	Dermal/Oc		520	(slightly irritated)			Lehman 1955
INTERMEDIATE EXPOSURE								
Death								
Rabbit	90d 1x/d					4200	(LD_{50})	Lehman 1955
Systemic								
Rabbit	90d 1x/d	Renal	2100	4200	(kidney damage)			Lehman 1955

d = day(s); (F) = feed; LD_{50} = lethal dose, 50%; LOAEL = lowest-observed-adverse-effect level; mg/kg/day = milligram per kilogram per day; NOAEL = no-observed-adverse-effect level; Oc = ocular; x = time

3.2.3.3 Immunological and Lymphoreticular Effects

Di-*n*-butyl phthalate does not appear to be a skin sensitizer. A variety of cosmetic materials (e.g., deodorants, nail polish) containing 4.5–9% di-*n*-butyl phthalate were not skin sensitizers when tested on 50–250 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 regarding the following health effects in humans or experimental animals after dermal exposure to di-*n*-butyl phthalate were located:

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

No relevant studies for other routes of exposure were located.

3.3 GENOTOXICITY

Genotoxic Effects. Available *in vitro* genotoxicity data are summarized in Table 3-3. Di-*n*-butyl phthalate has tested negative or marginally positive in prokaryotic (Agarwal et al. 1985; Seed 1982) and eukaryotic (Barber et al. 2000) gene mutation, chromosomal aberration (Ishidate and Odashima 1977), and DNA damage (Kleinsasser et al. 2000) 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.

Table 3-3. Genotoxicity of Di-n-butyl Phthalate *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	–	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:				
Saccharomyces cerevisiae	Gene mutation	–	–	Shahin and Von Borstel 1977
Mammalian cells:				
Human oropharyngeal mucosa	Single-strand DNA breaks	No data	+	Kleinsasser et al. 2000
Human nasal mucosa	Single-strand DNA breaks	No data	+	Kleinsasser et al. 2000
Mouse lymphoma	Gene mutation	+	–	Barber et al. 2000
Mouse lymphoma	Gene mutation	+	–	Hazleton Biotechnologies 1986
Chinese hamster ovary cells	Chromosomal aberrations	No data	(+)	Ishidate and Odashima 1977
Balb 3T3	Cell transformation	No data	–	Barber et al. 2000
Balb 3T3	Cell transformation	No data	–	Litton Bionetics 1985a

– = negative result; (+) = marginally positive; + = positive result

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No studies regarding absorption in humans after inhalation exposure to di-*n*-butyl phthalate were located. The relatively low concentration of di-*n*-butyl phthalate found in the lungs of rats exposed to 50 mg/m^3 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.

3.4.1.2 Oral Exposure

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

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, 63–97% 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, 85–100% 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 73% 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, mono-*n*-butyl phthalate, is probably the main form absorbed through the intestine (Lake et al. 1977; Takahashi and Tanaka 1989).

3.4.1.3 Dermal Exposure

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

In rats, approximately 60% of a single dermal dose of 157 µmol/kg was excreted in the urine during a 7-day period (the di-*n*-butyl phthalate remained on the skin for 7 days). The rate of di-*n*-butyl phthalate excretion (percentage of dose in 24 hours) remained constant over 7 days at 10–12% (Elsisi et al. 1989). The *in vitro* rate of dermal absorption in rats has been shown to be much greater than in humans (human skin absorption was 0.8% that of rat skin) (Scott et al. 1987).

3.4.2 Distribution

There are no data on the distribution of di-*n*-butyl phthalate in humans. Animal data suggest that following inhalation, oral, or dermal exposure, di-*n*-butyl phthalate is widely distributed throughout the body and does not accumulate in the body. There are no data on transplacental transfer or transfer via maternal milk. There is some evidence to suggest that di-*n*-butyl phthalate and its metabolites are rapidly cleared from the body (Foster et al. 1982; Tanaka et al. 1978; Williams and Blanchfield 1975). Thus, it is unlikely that di-*n*-butyl phthalate will be stored in maternal tissues and released during pregnancy or lactation.

3.4.2.1 Inhalation Exposure

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

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 50 mg/m^3 (Kawano 1980b). After 6 months of exposure, the highest concentrations were found in brain, followed by lung, kidney, liver, and testicles (Kawano 1980b). Organ concentrations varied considerably between rats. At exposure to 0.5 mg/m^3, di-*n*-butyl phthalate was consistently detected only in brains of exposed rats (Kawano 1980b).

3.4.2.2 Oral Exposure

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

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 4–48 hours after dosing showed no accumulation. At all of the time points evaluated, no organ contained >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).

Following a single oral dose of 1,500 mg/kg [^{14}C]-di-*n*-butyl phthalate to pregnant rats on gestational day 14, the amount of radioactivity in the embryo peaked at 0.12% of the total administered dose at 6 hours postdosing, and thereafter rapidly declined to undetectable levels (Saillenfait et al. 1998).

3.4.2.3 Dermal Exposure

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

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 43.6 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% was in muscle, and 0.41% was in adipose tissue. All other tissues combined contained <0.5% of the dose. About 33% of the dose remained at the site of application.

3.4.3 Metabolism

There is no direct evidence in humans or animals that the metabolism of di-*n*-butyl phthalate differs between adults and children. However, the activity of glucuronosyltransferase, a phase II enzyme involved in the biotransformation of mono-*n*-butyl phthalate to mono-*n*-butyl phthalate glucuronide, differs between adults and infants; adult activity is achieved at 6–18 months of age (Leeder and Kearns 1997).

3.4.3.1 Inhalation Exposure.

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

3.4.3.2 Oral Exposure

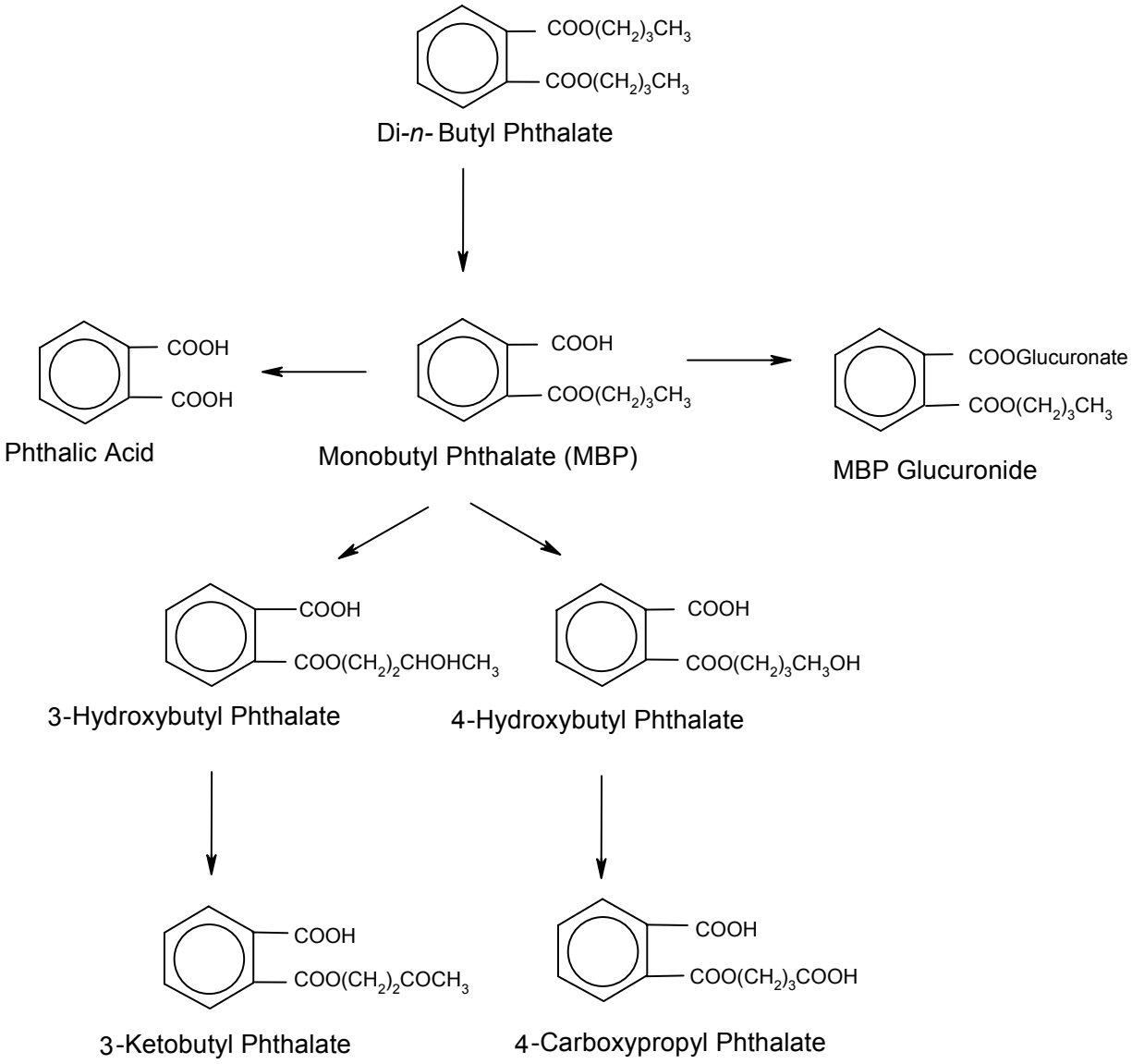
No studies regarding di-*n*-butyl phthalate metabolism in humans were located. Studies in animals indicate that metabolism of di-*n*-butyl phthalate proceeds mainly by hydrolysis of one butyl ester bond to yield mono-*n*-butyl phthalate. The product that appears in the urine is mainly mono-*n*-butyl phthalate conjugated with glucuronic acid, with lower levels of unconjugated mono-*n*-butyl phthalate, various oxidation products of mono-*n*-butyl phthalate (see Figure 3-2), and a small amount of the free phthalic acid (Figure 3-2) (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 mono-*n*-butyl phthalate than hamsters, in 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 3.2.2.6 Developmental Effects).

3.4.3.3 Dermal Exposure

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

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



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

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

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

3.4.4.2 Oral Exposure

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

Studies in laboratory animals (rats, hamsters, and guinea pigs) indicate that 63–97% of an oral dose of di-*n*-butyl phthalate is eliminated in the urine within 24 hours, with 85–100% 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)

3.4.4.3 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.

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

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various

combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

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

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

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994).

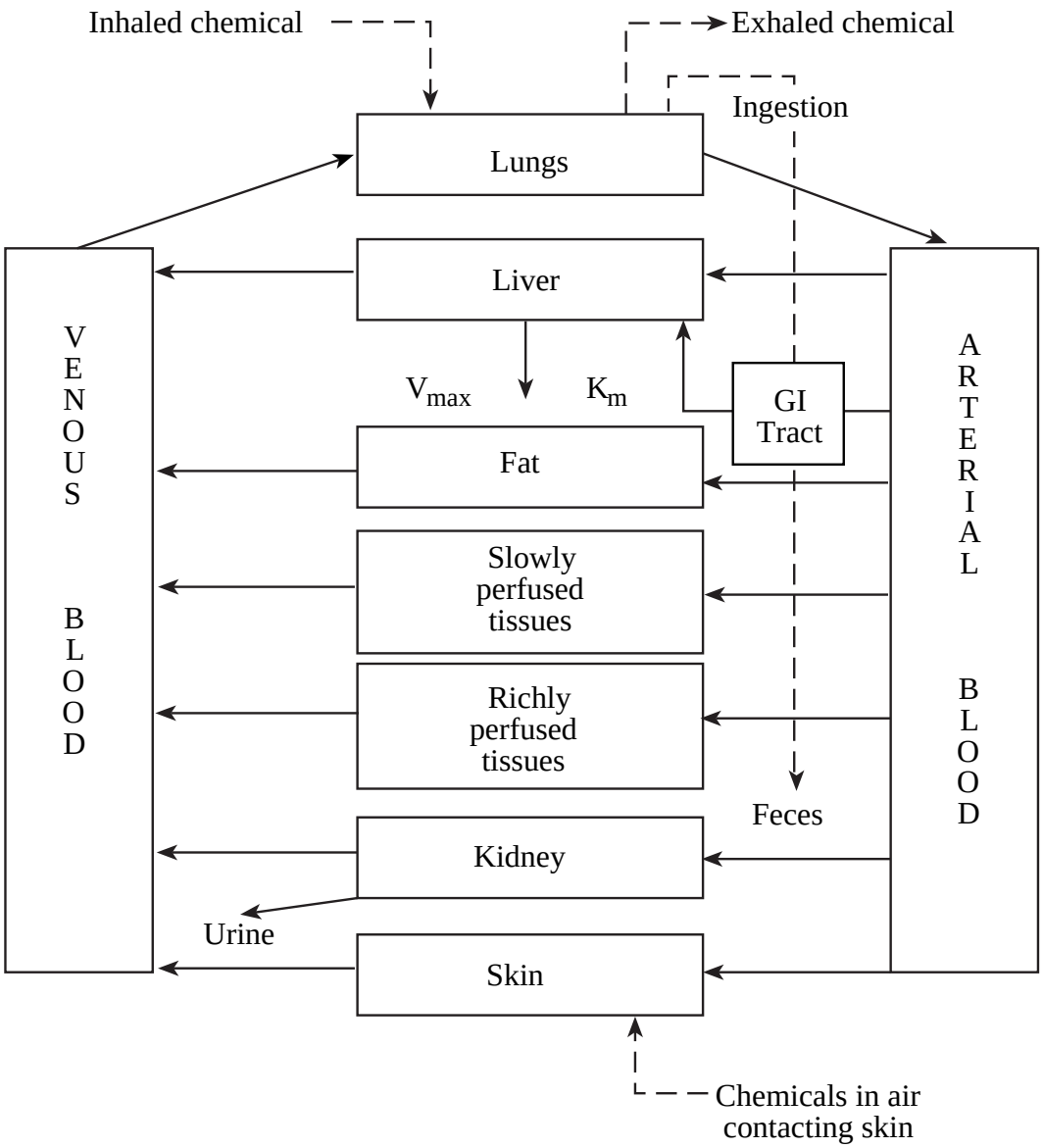
PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

Keys et al. (2000) describe a PBPK model of di-*n*-butyl phthalate in rats that simulates the pharmacokinetics of both di-*n*-butyl phthalate and its major metabolite, mono-*n*-butyl phthalate. The model is intended for use in simulating doses of mono-*n*-butyl phthalate to the testes resulting from oral exposures to di-*n*-butyl phthalate. It is based on a earlier model developed for simulating the pharmacokinetics of di(2-ethylhexyl) phthalate and mono(2-ethylhexyl) phthalate (Keys et al. 1999).

Description of the Model. The Keys et al. (2000) model simulates seven tissue compartments: small intestine, blood, liver, fat, testis, slowly perfused tissues, and rapidly perfused tissues. The model simulates the absorption of mono-*n*-butyl phthalate formed from di-*n*-butyl phthalate in the small intestine; absorption of intact di-*n*-butyl phthalate is assumed not to occur. Conversion of di-*n*-butyl phthalate to mono-*n*-butyl phthalate in the small intestine is simulated with a first order rate constant. Absorption of mono-*n*-butyl phthalate from the small intestine is simulated with a first order rate constant for uptake into the liver. Elimination of absorbed mono-*n*-butyl phthalate is assumed to be entirely by metabolism in the liver. Metabolism of mono-*n*-butyl phthalate is simulated with a single Michaelis-Menten-type function (i.e., k_m and V_{max}), which represents all pathways combined.

Keys et al. (2000) explored five approaches to modeling the pharmacokinetics of di-*n*-butyl phthalate and mono-*n*-butyl phthalate. In a flow-limited version of the model, transfers between blood and tissues are simulated as functions of blood flow, tissue concentrations of di-*n*-butyl phthalate or mono-*n*-butyl phthalate, and tissue:blood partition coefficients, assuming instantaneous partitioning of the compounds between tissue and blood (Ramsey and Anderson 1984). In an *enterohepatic circulation* version of the model, the transfer of mono-*n*-butyl phthalate from the liver to the small intestine is represented with a first order rate constant (diffusion-limited) and a time delay constant for the subsequent reabsorption of mono-*n*-butyl phthalate from the small intestine. In a *diffusion-limited* version of the model, the tissue transfers include a first order rate term (referred to as the permeation constant) that relates the intracellular-to-extracellular concentration gradient to the rates of transfer. This model requires estimates of extracellular tissue volume (ECV) and intracellular volume (ICV); ECV is assumed to be equal to tissue blood volume and ICV is assumed to be equal to the difference between tissue blood volume and

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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

total tissue volume. This approach would be expected to underestimate the true ECV of most tissues, which is approximately 45% of tissue mass (Edelman and Leibman 1959), and overestimate the true ICF; the significance of these potential differences are not discussed by Keys et al. (2000). In a *pH-trapping* version of the model, instantaneous partitioning (i.e., flow-limited) of only the nonionized species of mono-*n*-butyl phthalate between the intracellular and extracellular compartments of tissues is assumed, and the respective concentrations of the nonionized and ionized species in each compartment are predicted by the pK_a for the carboxylic acid moiety of mono-*n*-butyl phthalate (pK_a is assumed to be 3.79, and intracellular pH is assumed to be approximately 7.0). In a *diffusion-limited, pH-trapping* version of the model, mono-*n*-butyl phthalate is assumed to ionize and reach equilibrium with its nonionized form, as in the pH trapping version; however, the rate of partitioning of the nonionized mono-*n*-butyl phthalate from the extracellular to the intracellular compartment of the tissue is controlled by the permeation coefficient-surface area-cross product (diffusion-limited). In the intracellular compartment, mono-*n*-butyl phthalate is assumed to equilibrate, where it was mostly ionized. The permeation coefficient-surface area-cross product combined with the nonionized mono-*n*-butyl phthalate tissue:blood partition coefficients control the rate at which nonionized mono-*n*-butyl phthalate is predicted to leave the intracellular compartment.

Tissue:blood partition coefficients for total and nonionized mono-*n*-butyl phthalate were estimated from their n-octanol:water partition coefficients (K_{ow}), using the approach reported by Poulin and Krishnan (1995). Tissue:blood partition coefficients for total mono-*n*-butyl phthalate (ionized and nonionized) were determined experimentally using a vial-equilibration method with correction for pH (Table 3-4).

Keys et al. (2000) note that certain model parameter values were estimated by applying a step-wise parameter optimization routine to data on blood or tissue levels following oral or intravenous exposure to di-*n*-butyl phthalate and mono-*n*-butyl phthalate. The parameters estimated included the k_m and V_{max} values for metabolism of mono-*n*-butyl phthalate in the liver, the first order rate constant for the metabolism of di-*n*-butyl phthalate in the intestine, the first-order rate constant for absorption of mono-*n*-butyl phthalate from the small intestine, intracellular-to-extracellular transfer constants (e.g., permeation coefficient-surface-area-cross product) of nonionized mono-*n*-butyl phthalate, and biliary transfer of mono-*n*-butyl phthalate from liver to small intestine (these values are not provided in the profile because they are derived from optimization procedures and may not be directly useful for other models). Keys et al. (2000) do not explicitly cite or describe the data sets used to optimize model

Table 3-4. Tissue:Blood Partition Coefficients Used in the Keys et al. (2000) Model

Tissue	Nonionized mono-*n*-butyl phthalate (estimated)[a]	Total mono-*n*-butyl phthalate (experimental)[b]	Total mono-*n*-butyl phthalate (estimated)[c]
Liver	15.8	1.22 ± 0.25	0.9
Fat	313.0	0.05 ± 0.5	0.9
Muscle	4.6	Negative	1.9
Testes	4.9	1.9 ± 0.21	4.9

[a]from K_{ow} based on algorithms from Poulin and Krishnan (1995); used for the pH trapping and combined diffusion limited-pH trapping models
[b]vial equilibration study with pH correction
[c]from K_{ow} at physiological pH (largely ionized) based on algorithms from Poulin and Krishnan (1995); used for the flow limited, enterohepatic circulation, and diffusion limited models

parameter values. Based on Table 4 of their report, it appears that at least some data from National Institute of Environmental Health Sciences (NIEHS) (1994, 1995) were used to optimize the model.

Validation of the Model. Outputs from the various models were compared to observations of blood concentrations reported from studies of oral gavage or intravenous exposures of rats to di-*n*-butyl phthalate (NIEHS 1994, 1995). Based on the comparisons of model outputs to observed time courses for blood mono-*n*-butyl phthalate concentrations from NIEHS (1994, 1995), Keys et al. (2000) concluded that the *diffusion-limited, pH-trapping* model more closely represents the empirical data. However, it is difficult to interpret this finding if the same data were used in the model optimization (see Table 4 of Keys et al. 2000). The *diffusion-limited, pH-trapping* model simulated reasonably well the time courses for blood concentrations of mono-*n*-butyl phthalate reported by NIEHS (1994, 1995). A log-likelihood ratio test was used to compare the fit of the various augmented models to that of the flow-limited model. The *diffusion-limited, pH-trapping* model gave a better statistical fit to the empirical data than the other four models, with the next best fit achieved with enterohepatic circulation model. However, the latter model appeared to underestimate peak mono-*n*-butyl phthalate plasma concentrations, which would be an important limitation for its use in risk assessment.

Risk Assessment. The model provides an approach to estimating doses of mono-*n*-butyl phthalate to the testes of the rat following oral doses of di-*n*-butyl phthalate and may be useful for internal dose-response assessment of rat bioassay data in which the toxicity end point of interest is testicular toxicity. However, such uses of the model, or other potential uses in risk assessment, have not been evaluated.

Target Tissues. Output from the model, for which validation exercises were conducted, are predictions of blood and testes concentrations of mono-*n*-butyl phthalate.

Species Extrapolation. The model is designed to predict the blood and testes concentrations of mono-*n*-butyl phthalate following oral doses of di-*n*-butyl phthalate to rats. Extrapolation to other species would require modification of the model to account for different tissue masses, blood flows, and possibly other kinetic variables.

Interroute Extrapolation. The model is designed to simulate the pharmacokinetics of di-*n*-butyl phthalate and its metabolite, mono-*n*-butyl phthalate, when exposure is by the oral route. The pharmacokinetics of di-*n*-butyl phthalate would be expected to be different for other routes of exposure; therefore, the output of the model cannot be extrapolated to other routes (e.g., dermal, inhalation) without modification of the model. Calibration and validation studies utilized gavage exposures for oral dosing, and therefore, the model may not be applicable to other oral exposure pathways (e.g., dietary, drinking water) without modification.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

There is good evidence that following oral exposure, di-*n*-butyl phthalate is metabolized to mono-*n*-butyl phthalate and butanol by nonspecific esterases in the gastrointestinal tract (Cater et al. 1977; Lake et al.1977; Takahashi and Tanaka 1989). The results of studies by Fukuoka et al. (1995) and Zhou et al. (1990) suggest that mono-*n*-butyl phthalate may be the chemical responsible for the testicular toxicity of di-*n*-butyl phthalate.

3.5.2 Mechanisms of Toxicity

The most characteristic effect of di-*n*-butyl phthalate in animal models is the effect on the testes, in particular the testicular atrophy observed following acute- (Cater et al. 1977; Fukuoka et al. 1989, 1990; Gray and Gangolli 1986; Oishi and Hiragi 1980b) or intermediate- (Gray et al. 1999; NTP 1995; Srivastava et al. 1990) duration exposure or *in utero*/lactational exposure (IRDC 1984; Mylchreest et al. 1998b, 2000; NTP 1995). The testicular atrophy is characterized by sloughing of germ cells as early as 6-hours post exposure (Fukuoka et al. 1990), ultimately resulting in seminiferous tubules with only Sertoli cells.

Fukuoka and associates have conducted a series of studies to elucidate the mechanism of testicular toxicity (Fukuoka et al. 1989, 1990, 1993, 1994, 1995; Zhou et al. 1990). One proposed mechanism of toxicity involves a disturbance in the interaction between germ cells and Sertoli cells. The Sertoli cell-germ cell interaction is generally considered to be required for the differentiation of male germ cells and their progression through the seminiferous epithelium and release as mature spermatozoa. Exposure to

di-*n*-butyl phthalate is associated with both the release of iron from hemoglobin and/or transferrin in the liver and spleen, and the subsequent depletion of iron in the blood and testes. The decreased amount of available iron results in a decrease in succinate dehydrogenase activity in the Sertoli cells, resulting in disturbances in the energy transfer system between Sertoli cells and germ cells; anoxia due to iron depletion and/or disturbances in the energy supply may induce the sloughing of germ cells. Decreases in testicular sorbitol, fructose, and glucose levels have been observed in the testes 3–12 hours post exposure. Two days after exposure, there were significant decreases in sorbitol dehydrogenase and succinate dehydrogenase activities and decreases in testicular iron and zinc levels. Another mechanism of toxicity proposed for all phthalate esters that cause testicular toxicity involves interference with the interaction of follicle stimulating hormone (FSH) with the FSH receptor on Sertoli cells (NTP 2000). This mechanism may be applicable to di-*n*-butyl phthalate, but no studies regarding this mechanism and di-*n*-butyl phthalate were located. It is likely that mono-*n*-butyl phthalate, the primary metabolite of di-*n*-butyl phthalate, is responsible for the testicular toxicity.

3.5.3 Animal-to-Human Extrapolations

Species differences in the testicular toxicity of di-*n*-butyl phthalate have been observed. Severe testicular atrophy has been observed in rats and guinea pigs orally exposed to di-*n*-butyl phthalate. In mice exposed to the same oral dose, focal testicular atrophy was observed, and no testicular effects were observed in hamsters (Gray et al. 1982). The basis for the species differences is not known, but could be related to species differences in the free concentration of the primary metabolite of di-*n*-butyl phthalate, mono-*n*-butyl phthalate (Foster et al. 1982). In rats, the levels of mono-*n*-butyl phthalate and di-*n*-butyl phthalate and β-glucuronidase activity in the testes were markedly higher than in hamsters. Foster et al. (1982) suggested that the rate of mono-*n*-butyl phthalate glucuronide hydrolysis in rats is higher than in hamsters resulting in increased mono-*n*-butyl phthalate levels in the rat testes. There are insufficient data to assess whether rats, mice, or hamsters would be an appropriate animal model for testicular toxicity in humans.

Studies in nonhuman primates with phthalate esters (primarily di-isononyl phthalate and di-2-ethylhexyl phthalate) have shown no hepatic effects similar to those seen in rodents, including peroxisome proliferation (Astill 1989; Pugh et al. 2000; Rhodes et al. 1986; Short et al. 1987); this suggests that primates, including humans, are probably not sensitive to the hepatic effects of peroxisome proliferators.

3.6 ENDOCRINE DISRUPTION

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Phthalates are a class of chemicals that have been implicated as having estrogenic properties. There is both *in vitro* and *in vivo* evidence of the weak estrogenic behavior of di-*n*-butyl phthalate. The results of three *in vitro* assays provide evidence of weak estrogenic activity. The first study used the recombinant yeast screening test to assess estrogenic activity (Harris et al. 1997). In this test, a gene for human estrogen receptor is integrated into the main yeast genome and is expressed in a form capable of binding to estrogen response elements and controlling the expression of the reporter gene lac-Z; when the lac-Z gene is expressed, β-galactoside is produced. Harris et al. (1997) found a dose-dependent increase in β-galactosidase production suggesting that di-*n*-butyl phthalate had some estrogenic activity. However, the di-*n*-butyl phthalate was approximately 10-million-fold less potent than estradiol. Di-*n*-butyl phthalate also induced proliferation of MCF-7 and ZR-75 human breast cancer cell lines (Harris et al. 1997). Zacharewski et al. (1998) found that di-*n*-butyl phthalate induced reporter gene (luciferase) activity in MCF-7 human breast cancer cells, but not HeLa human cervical carcinoma cells, transfected with human estrogen receptor, although approximately 3,000-fold less potent than 17β-estradiol. Additionally, Zacharewski et al. (1998) found that di-*n*-butyl phthalate was capable of supporting a very

modest amount of growth in an estrogen-dependent recombinant yeast strain. Jobling et al. (1995) found that di-*n*-butyl phthalate reduced the binding of 17β-estradiol to the fish estrogen receptor and stimulated the transcriptional activity of the estrogen receptor. Zacharewski et al. (1998) found that di-*n*-butyl phthalate was also capable of competing weakly with 17β-estradiol for binding to Sprague-Dawley rat uterine estrogen receptor *in vitro*, although over 36,000 times weaker than 17β-estradiol. However, differences in the kinetics of displacement of estrogen from the fish and rat estrogen receptors by di-*n*-butyl phthalate may indicate significant species differences between estrogen receptors for binding di-*n*-butyl phthalate (Jobling et al. 1995; Zacharewski et al. 1998). Although the results of the *in vitro* studies consistently suggest that di-*n*-butyl phthalate has estrogenic properties, the *in vivo* data do not provide supportive evidence for di-*n*-butyl phthalate estrogenicity. This may be due, at least in part, to the presence *in vivo* of esterases that metabolize di-*n*-butyl phthalate to mono-*n*-butyl phthalate, which has been reported not to interact with the estrogen receptor (Mylchreest et al. 1998b). An acute *in vivo* assay by Milligan et al. (1998) did not find a significant increase in uterine vascular permeability in ovariectomized mice 4 hours after subcutaneous administration of 927 mg/kg di-*n*-butyl phthalate. In contrast to 17β-estradiol, di-*n*-butyl phthalate did not affect body weight, induce an increase in uterine wet weight, or induce vaginal cornification in ovariectomized rats treated orally with up to 2,000 mg/kg/day di-*n*-butyl phthalate for 4 days (Zacharewski et al. 1998). Likewise, di-*n*-butyl phthalate did not induce lordosis behavior or increased uterine weight in ovariectomized rats after exposure for 2 days, followed by 0.5 mg progesterone (Gray et al. 1999). Ema et al. (2000a) found that di-*n*-butyl phthalate failed to induce a decidual cell response in rats. Pseudopregnant rats (females bred to vasectomized males) treated di-*n*-butyl phthalate on days 0–8 of pseudopregnancy, followed by surgical induction of the decidual cell response had lower ovarian weights, uterine weights, and serum progesterone levels on day 9 of pseudopregnancy, compared to controls, indicating a lack of estrogenic activity. However, the results of the NTP (1995) multigeneration study, particularly the finding that the reproductive effects in the first generation males appeared more adverse than those in the parental generation (see Sections 2.2.2.5 Reproductive Effects and 3.2.2.6 Developmental Effects for a description of these effects), are suggestive that di-*n*-butyl phthalate can disrupt normal male development. Additionally, the decreases in anogenital distance observed in rat fetuses (Ema et al. 1998, 2000b; Mylchreest et al. 1999, 2000) suggest that di-*n*-butyl phthalate has anti-androgenic properties. This is further supported by the findings of Gray et al. (1999), showing similar, but not identical, effects from di-*n*-butyl phthalate exposure as from exposure to linuron, a known androgen receptor ligand. These effects included delayed preputial separation, reduced fertility, testicular atrophy, and reduced sperm production in treated males, and reduced anogenital distance, increased number of retained nipples, and

decreased androgendependent tissue weights in male offspring (exposed *in utero* and via lactation only) of treated rats. However, these androgen-related effects do not appear to be mediated by interaction of di-*n*-butyl phthalate or its primary metabolite, mono-*n*-butyl phthalate, with the androgen receptor (Mylchreest et al. 1998b, 1999) (see Section 3.5.2 Mechanisms of Toxicity for a discussion of the possible mechanism of androgen disruption). Di-*n*-butyl phthalate is known to be a testicular toxicant. One mechanism of toxicity proposed for all phthalate esters that cause testicular toxicity involves interference with the interaction of follicle stimulating hormone (FSH) with the FSH receptor on Sertoli cells (NTP 2000). This mechanism may be applicable to di-*n*-butyl phthalate, but no studies regarding this mechanism and di-*n*-butyl phthalate were located.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 5.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example,

infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

No information on the toxicity of di-*n*-butyl phthalate in children was located, and there is a limited amount of data in adults. The available oral-exposure animal studies clearly demonstrate that the developing organism is sensitive to the toxicity of di-*n*-butyl phthalate. Postimplantation losses and decreases in the number of live fetuses have been observed in a number of acute-duration studies in which rats received gavage doses of 630 mg/kg/day and higher on gestational days 0–8, 7–15, 7–9, 10–12, 13–15, or 6, 8, 10, 12, 13, 14, 15, or 16 (Ema et al. 1993, 1994, 1995, 1997a, 2000a) or in mice receiving gavage doses of 2,500 mg/kg/day on gestational days 6–13 (Hardin et al. 1987). Decreases in the number of live pups per litter have also been observed in intermediate-duration studies in which rats or mice were exposed to 80 or 1,950 mg/kg/day, respectively, throughout gestation, lactation, and postweaning (NTP 1995), or rats were exposed to 250–500 mg/kg/day *in utero* and during lactation (Gray et al. 1999). Decreases in fetal/pup body weight have been observed in rats receiving gavage doses of 500 mg/kg/day

or higher di-*n*-butyl phthalate on gestational days 0–8 (Ema et al. 2000a), 630 or 750 mg/kg/day on gestational days 7–15, 7–9, 10–12, 13–15, 6, 7, 8, 9, 10, 11, or 16 (Ema et al. 1994, 1995, 1997a), and in rats and mice exposed to 240 or 460 mg/kg/day, respectively, in the diet throughout gestation, lactation, and postnatal days 28–56 (NTP 1995). Skeletal (primarily fusion of cervical vertebrae) and external (cleft palate) malformations have been observed in rats receiving gavage doses of 750 mg/kg/day on gestational days 7–9 or 13–15 (Ema et al. 1994, 1995). Impaired development of the reproductive system has also been observed in an acute-duration study (Ema et al. 1998) and in several intermediate-duration studies (IRDC 1984; Mylchreest et al. 1998b; NTP 1995). Ema et al. (1998) reported an increased incidence of undescended testes and decreased anogenital distance in the offspring of rats receiving gavage doses of 555 mg/kg/day and higher on gestational days 11–21. The reproductive effects observed in the intermediate-duration studies are similar to the effects observed in adult animals exposed to di-*n*-butyl phthalate. Decreases in reproductive organ weights, testicular degeneration/ atrophy, and hypospermia have been observed in the offspring of rats exposed throughout gestation, lactation, and postnatally to 250 mg/kg/day and higher di-*n*-butyl phthalate (Gray et al. 1999; IRDC 1984; Mylchreest et al. 1998b, 2000; NTP 1995). More details about these studies can be found in Section 3.2.2.6 Developmental Effects.

NTP (1995) conducted two studies to assess the impact of perinatal exposure on the subchronic toxicity of di-*n*-butyl phthalate. In the first study, weanling rats and mice were exposed to dietary di-*n*-butyl phthalate for 13 weeks. In the second study, the 13-week dietary exposure was immediately preceded by gestational and lactational exposure. Similar effects, particularly decreases in body weight gain, hepatomegaly, and testicular degeneration/atrophy were observed in both studies; suggesting that the perinatal rat is neither resistant nor hypersensitive to the short-term toxic effects of di-*n*-butyl phthalate as compared to rats only exposed postnatally (NTP 1995).

No human or animal data were located that examined possible age-related differences in the toxicokinetics of di-*n*-butyl phthalate. However, it is known that one of the enzymes involved in phase II biotransformation of mono-*n*-butyl phthalate, the primary di-*n*-butyl phthalate metabolite, is influenced by age. Glucoronsyltransferase activity differs in adults and children under the age of 6–18 months (Leeder and Kearns 1997). Di-*n*-butyl phthalate and its primary metabolite, mono-*n*-butyl phthalate, have been detected in placental and embryonic tissues of treated pregnant rats (Saillenfait et al. 1998), with mono-*n*-butyl phthalate accounting for 50–95% of the total amount recovered. In the embryo, approximately 1% of the recovered mono-*n*-butyl phthalate was conjugated with glucuronic acid, but

approximately 10% was conjugated in maternal plasma and placenta; this may indicate limited transfer of conjugated mono-*n*-butyl phthalate to the embryo or an inability of embryonic tissues to conjugate mono-*n*-butyl phthalate. There are no data on the toxicokinetic properties of di-*n*-butyl phthalate in children or immature animals, or on transfer via maternal milk. Toxicokinetic information on di-*n*-butyl phthalate is sparse, but existing oral studies (Foster et al. 1982; Tanaka et al. 1978; Williams and Blanchfield 1975) indicate that di-*n*-butyl phthalate and its metabolites are rapidly cleared from the body. Thus, di-*n*-butyl phthalate from maternal preconception exposure is highly unlikely to be stored in maternal tissues and released during pregnancy or lactation.

Subsequent sections of this chapter (Sections 3.8, 3.9, and 3.11) discuss the available information on biomarkers, interactions, and methods for reducing toxic effects. The available information is from adults and mature animals; no child-specific information was identified. It is likely that this information will also be applicable to children.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as

copper, zinc, and selenium). Biomarkers of exposure to di-*n*-butyl phthalate are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by di-*n*-butyl phthalate are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10. “Populations that are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify 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; EPA 1986g), in lipid-rich atherosclerotic plaques (Ferrario et al. 1985), in seminal fluid (Murature et al. 1987), and in blood serum (Ching et al. 1981a; EPA 1986g). 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. No data were found on the concentration of the primary metabolite, mono-*n*-butyl phthalate, in human body tissues or fluids.

3.8.2 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 (Moody et al. 1991; Popp et al. 1989). These and other effects associated with di-*n*-butyl phthalate exposure do not appear to be sufficiently specific to serve as biomarkers of effects.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Administration of zinc provides some protection against the testicular toxicity of di-*n*-butyl 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.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to di-*n*-butyl phthalate than will most persons exposed to the same level of di-*n*-butyl phthalate in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of di-*n*-butyl phthalate, or compromised function of organs affected by di-*n*-butyl phthalate. Populations who are at greater risk due to their unusually high exposure to di-*n*-butyl phthalate are discussed in Section 6.7 Populations with Potentially High Exposures.

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 animal studies, a number of developmental effects were reported, including postimplantation losses, decreases in the number of live fetuses, decreases in fetal/pup body weight, increases in the incidence of external and skeletal malformations, and impaired development of the reproductive system (Ema et al. 1993, 1994, 1995a, 1997a, 1998, 2000a, 2000b; Gray et al. 1999; IRDC 1984; Mylchreest et al. 1998b, 1999, 2000; NTP 1995). In most of these studies, the developmental

effects were at dietary or gavage levels which were not associated with maternal toxicity. 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. Some studies suggested that pregnant rats may be more susceptible to the lethal effects of di-*n*-butyl phthalate. A more detailed discussion of children's susceptibility can be found in Section 3.7.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to di-*n*-butyl phthalate. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to di-*n*-butyl phthalate. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

No texts were found that provided specific information about treatment following exposures to di-*n*-butyl phthalate

3.11.1 Reducing Peak Absorption Following Exposure

Methods for reducing peak absorption of di-*n*-butyl phthalate include gut dilution, eye irrigation, and washing with soap (Ellenhorn 1997). No information regarding ways to reduce absorption following inhalation exposure was located.

3.11.2 Reducing Body Burden

No experimental data regarding methods for reducing the di-*n*-butyl phthalate body burden were located. The available toxicokinetic data suggest that di-*n*-butyl phthalate is rapidly cleared from the body. Twenty-four hours after dosing, 63–97% of an oral dose is excreted in the urine (Foster et al. 1982; Tanaka et al. 1978; Williams and Blanchfield 1975).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No methods which would interfere with mechanism of di-*n*-butyl phthalate toxic were identified.

3.12 ADEQUACY OF THE DATABASE

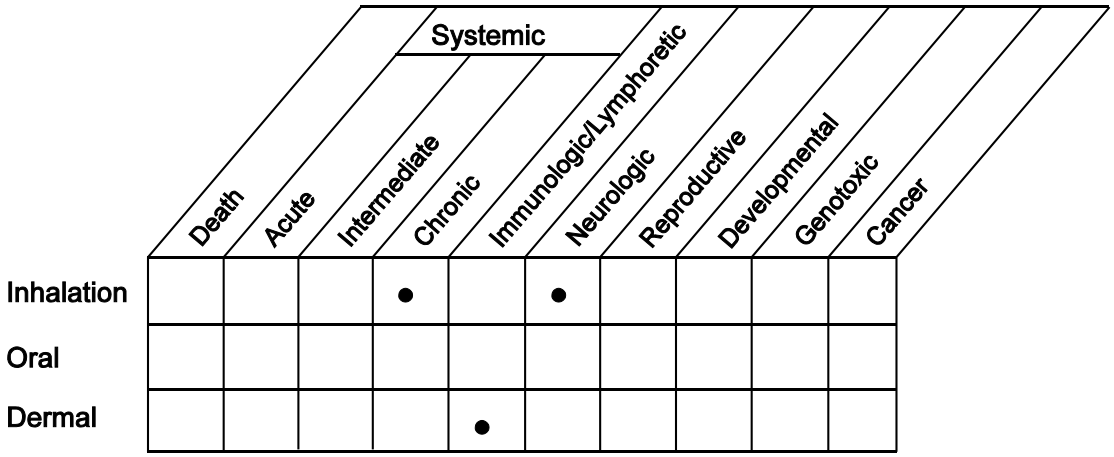
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of di-*n*-butyl phthalate is available. Where adequate information 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 the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

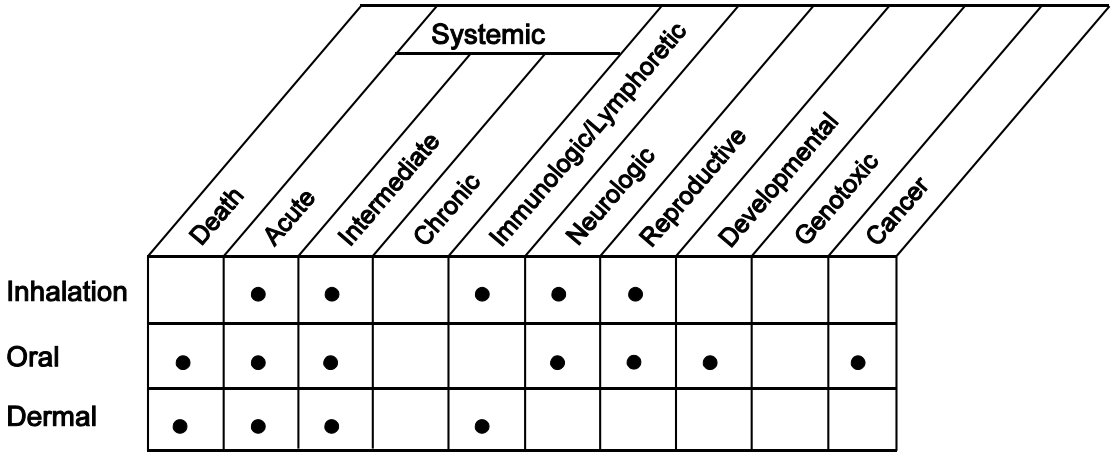
3.12.1 Existing Information on Health Effects of Di-*n*-butyl Phthalate

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 3-4. 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 necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 3-4. Existing Information on Health Effects of Di-*n*-butyl Phthalate



Human



Animal

● Existing Studies

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.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. No information regarding health effects of di-*n*-butyl phthalate in humans was located. Animal studies that have examined the acute toxicity of orally administered di-*n*-butyl phthalate have primarily focused on reproductive (Cater et al. 1977; Fukuoka et al. 1989, 1990; Gray et al. 1982; Oishi and Hiraga 1980b; Tanino et al. 1987) and developmental (Ema et al. 1993, 1994, 1995a, 1997b, 1998; Saillenfait et al. 1998) end points. An acute-duration oral MRL was derived from a NOAEL for developmental effects (Mylchreest et al. 2000). The systemic toxicity of di-*n*-butyl phthalate has not been adequately assessed. No information concerning target organs following acute-duration inhalation or dermal exposure to di-*n*-butyl phthalate in animals or humans was located, 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 are needed to assess the risks to populations surrounding hazardous waste sites that might be exposed to di-*n*-butyl phthalate for brief periods.

Intermediate-Duration. No human data on the toxicity of di-*n*-butyl phthalate following intermediate-duration exposure were identified. Systemic, reproductive, and developmental effects have been observed in animals following oral exposure. The liver appears to be the most sensitive systemic target in rats and mice exposed to di-*n*-butyl phthalate in the diet for 13 weeks (NTP 1995; Schilling et al. 1992). The reproductive effects consist of testicular atrophy with decreases in spermatogenesis (Murakami et al. 1986a, 1986b; NTP 1995; Srivastava et al. 1990), and the developmental effects included decreases in the number of pups per litter in rats and impaired reproductive development in male offspring (NTP 1995). An intermediate-duration oral MRL was not derived because the lowest LOAEL was identified for a serious effect and the study did not identify a NOAEL. A toxicity study

identifying a NOAEL for developmental effects are needed for assessing risk for populations living near hazardous waste sites.

No intermediate-duration inhalation studies were identified. These data are needed for assessing risk associated with exposure to inhaled di-*n*-butyl phthalate. The only intermediate-duration dermal study (Lehman 1955) examined a very limited number of end points and would have limited usefulness for assessing hazard and risk following dermal exposure to di-*n*-butyl phthalate.

Chronic-Duration Exposure and Cancer. No information concerning the toxic effects of chronic-duration exposure to di-*n*-butyl phthalate in humans or animals by any route of exposure was located. 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 are needed 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 regarding the carcinogenicity of di-*n*-butyl phthalate in humans or animals was located.

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 are needed to determine whether di-*n*-butyl phthalate has mutagenic potential and, if so, what the possible mechanism of genotoxicity might be.

Reproductive Toxicity. No data on the reproductive toxicity of di-*n*-butyl phthalate in humans were located. Testicular atrophy and decreased fertility have been observed in orally-exposed animals (Cater et al. 1977; Fukuoka et al. 1989, 1990; Gray et al. 1982; Oishi and Hiraga 1980b; Tanino et al. 1987). Species differences are apparent, with rats and guinea pigs being more sensitive than mice, and hamsters being relatively insensitive to this effect (Gray et al. 1982). The species differences may be related to an increased ability to hydrolyze mono-*n*-butyl phthalate glucuronide resulting in increased levels of free mono-*n*-butyl phthalate and testicular toxicity. Information that could be used to determine which animal species would be a good model for testicular toxicity in humans would be useful in assessing risk in humans exposed to di-*n*-butyl phthalate. Further, studies administering chronic low levels of di-*n*-butyl phthalate are needed to determine whether or not any reproductive impairment or endocrine

disruption occurs at background levels. Additionally, it is not known if testicular effects would also be a sensitive end point following inhalation or dermal exposure.

Developmental Toxicity. No human developmental toxicity studies were located. Studies in rats and mice have shown that oral exposure to di-*n*-butyl phthalate can result in a number of developmental effects including postimplantation loss, decreases in the number of live births/litter, external, internal, and skeletal malformations, and impaired development of the reproductive system in male offspring (Ema et al. 1993, 1994, 1995a, 1997b, 1998, 2000a, 2000b; Gray et al. 1999; IRDC 1984; Mylchreest et al. 1998b, 1999, 2000; NTP 1995; Saillenfait et al. 1998). Although a number of studies have examined the developmental toxicity of di-*n*-butyl phthalate, NOAELs have not been identified for some of the more sensitive developmental effects, such as decreases in the number of live births and impaired development of the reproductive system, following intermediate-duration oral exposure. Identification of NOAELs for these effects are needed to establish an intermediate-duration oral MRL for di-*n*-butyl phthalate. NTP (1995) conducted two studies to assess whether perinatal exposure increased the toxicity of di-*n*-butyl phthalate. The studies did not find any difference in terms of critical effects and doses; however, reproductive performance was not evaluated, and it is also not known if there would be any second generation developmental effects. Developmental end points have not been assessed in animals following inhalation or dermal exposure. Such studies are needed for extrapolating the possible risk to human populations exposed environmentally by these routes.

Immunotoxicity. The results from the available human and animal studies indicate that di-*n*-butyl phthalate is not a skin-sensitizing agent following dermal exposure (Lehman 1955; Schulsinger and Mollgaard 1980). These studies did not assess other aspects of immunotoxicity. Additionally, immunotoxicity has not been adequately assessed following inhalation or oral exposure. Tests of several additional end points of humoral and cell-mediated immune function are needed to assess the sensitivity of this system to di-*n*-butyl phthalate.

Neurotoxicity. The neurotoxic potential of di-*n*-butyl phthalate has not been adequately evaluated in human or animal studies. Neurotoxicity studies are needed to determine the hazards associated with human exposure to di-*n*-butyl phthalate.

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; blood and tissue levels were the primary end points examined (Ferrario et al. 1985; Mes et al. 1974; Schulsinger and Mollgaard 1980).

Studies of people occupationally exposed to di-*n*-butyl phthalate are needed to assess the effects of di-*n*-butyl phthalate on human health. Since one of the most significant effects in animals is testicular atrophy, 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.

Exposure. The presence and concentration of di-*n*-butyl phthalate can be measured in a variety of biological tissues and fluids, but no information that would allow correlation of body levels with source, route, amount, or duration of exposure to di-*n*-butyl phthalate was located. The primary metabolite of di-*n*-butyl phthalate in several species is mono-*n*-butyl phthalate, and so mono-*n*-butyl phthalate or its glucuronide conjugate could possibly serve as a biomarker of exposure to di-*n*-butyl phthalate. However, because mono-*n*-butyl phthalate is also a metabolite of butyl benzyl phthalate (Nativelle et al. 1999), it is not a specific biomarker for di-*n*-butyl phthalate. Therefore, studies that identify specific markers of exposure and determine the relationship between body levels of di-*n*-butyl phthalate and exposure are needed to develop methods for identifying and monitoring populations with high exposure to di-*n*-butyl phthalate.

Effect. 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 mono-*n*-butyl 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 are needed to evaluate 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, and on the enzymes involved in detoxification of di-*n*-butyl phthalate, especially glucuronosyltransferase, could help to understand the biological mechanisms behind the species differences in response to di-*n*-butyl phthalate.

Methods of Reducing Toxic Effects. Di-*n*-butyl phthalate is metabolized in the gastrointestinal tract by nonspecific esterases to form mono-*n*-butyl phthalate. Identification of substances that could inhibit this biotransformation and possibly reduce absorption or that would induce glucuronidation of mono-*n*-butyl phthalate would be valuable. There are no methods to block the toxic response due to exposure to di-*n*-butyl phthalate or to mitigate the observed health effects.

Children's Susceptibility. No information on the toxicity of di-*n*-butyl phthalate in children has been located. Studies that examine sensitive end points such as reproductive, hematological, or hepatic effects in young animals would be useful for assessing whether children will be unusually susceptible to di-*n*-butyl phthalate toxicity. It is particularly important to conduct studies on chronic low level exposure of di-*n*-butyl phthalate because of its ubiquitous nature in many everyday items. Further, research suggests di-*n*-butyl phthalate may have the capability to disrupt the endocrine system; such potential is especially critical in developing and prepubescent children. The available animal data suggest that the developing organism is sensitive to di-*n*-butyl phthalate toxicity. As discussed in Section 3.2.2.6, the observed developmental effects include postimplantation losses, decreases in the number of live fetuses per litter, decreases in fetal/pup body weights, increases in the incidences of external and skeletal malformations, and altered reproductive development in the offspring. Data needs relating to development are discussed

in detail in the Developmental Toxicity subsection above. There are no data on whether di-*n*-butyl phthalate can cross the placenta or be transferred to an infant via breast milk. Although there are no data on whether di-*n*-butyl phthalate is stored in maternal tissues and whether these stores can be mobilized during pregnancy or lactation, the rapid clearance of di-*n*-butyl phthalate in animals receiving a single oral dose suggests that di-*n*-butyl phthalate would not be stored in maternal tissues.

The available toxicokinetic data did not evaluate the potential differences between adults and children, although there is some evidence that there are age-related differences in the activity of at least one enzyme, UDP-glucoronsyltransferase, that is involved in the metabolism of di-*n*-butyl phthalate. Toxicokinetic studies examining how aging can influence the absorption, distribution, and excretion of di-*n*-butyl phthalate would be useful in assessing children's susceptibility to di-*n*-butyl phthalate toxicity. The mechanism of action for a number of toxic effects have not been elucidated. There are no data to determine whether there are age-specific biomarkers of exposure or effects or any interactions with other chemicals that would be specific for children. There is very little available information on methods for reducing di-*n*-butyl phthalate toxic effects or body burdens; it is likely that research in adults would also be applicable to children.

Child health data needs relating to exposure are discussed in Section 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

Ongoing studies pertaining to di-*n*-butyl phthalate have been identified and are shown in Table 3-5.

Table 3-5. Ongoing Studies on Di-*n*-butyl Phthalate

Investigator	Affiliation	Research description	Sponsor
Cunningham, ML	NIEHS, NIH	Evaluation of peroxisome proliferation-interspecies differences, induction of carcinogenicity	NIEHS
Pereira, MM	Medical College of Ohio	Effect of peroxisome proliferators on methylation of genes	NIEHS
Thomas, R	Florida A&M University	Genotoxicity of di-*n*-butyl phthalate	ATSDR

ATSDR = Agency for Toxic Substances and Disease Registry; NIEHS = National Institute of Environmental Health

4. CHEMICAL AND PHYSICAL INFORMATION

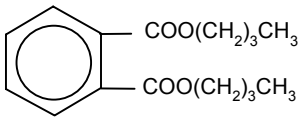
4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of di-*n*-butyl phthalate is located in Table 4-1. Table 4-1 lists common synonyms, trade names, and other pertinent identification information for di-*n*-butyl phthalate.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of di-*n*-butyl phthalate is located in Table 4-2. Table 4-2 lists important physical and chemical properties of di-*n*-butyl phthalate, but is not intended to be all inclusive.

Table 4-1. Chemical Identity of Di-*n*-butyl Phthalate

Characteristic	Information	Reference
Chemical name	Di-*n*-butyl phthalate	HSDB 2000
Synonym(s)	1,2-Benzenedicarboxylic acid, dibutyl ester; Butyl phthalate; DBP; Dibutyl-*o*-phthalate; Dibutyl phthalate; Phthalic acid butyl ester	HSDB 2000; Budavari 1996
Registered trade name(s)	Caswell No. 292; Celluflex DBP; Palatinol C; Polycizer DBP; PX 104; Staflex DBP; Uniflex DB	HSDB 2000
Chemical formula	$C_{16}H_{22}O_4$	Budavari 1996
Chemical structure		Metcalf 1994
Identification numbers:		
CAS Registry	84-74-2	Lewis 1993
NIOSH RTECS	TI0875000	HSDB 2000
EPA Hazardous Waste	U069	EPA 1992
OHM/TADS	7216617	CIS 1999
DOT/UN/NA/IMCO	UN 2810/NA 9095	DOT 1998
HSDB	922	HSDB 2000
NCI	5804	NIH 1999

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

Table 4-2. Physical and Chemical Properties of Di-*n*-butyl Phthalate

Property	Information	Reference
Molecular weight	278.34	Budavari 1996
Color	Colorless to faint yellow	HSDB 1999
Physical state	Oily liquid	Lewis 1993
Melting point	-35 EC	Verschueren 1996
Boiling point	340 EC	Budavari 1996
Density at 20 EC	1.04 kg/L	Ashford 1994
Odor	Slight ester-like	EPA 1993
Odor threshold:		
Water	No data	
Air	0.26–1.47 mg/m^3	EPA 1980b
Taste	Strong and bitter taste	HSDB 1999
Solubility:		
Water	11.2 mg/L	Staples et al. 1997
Freshwater at 20 EC	10.1–11.1 mg/L	Shiu et al. 1990
Organic solvent (s)	Very soluble in alcohol, ether, acetone, and benzene	Budavari 1996
Partition coefficients:		
Log K_{ow}	4.72	Hansch et al. 1995
	4.45	Staples et al. 1997
	3.7	de Bruijn et al. 1989
Log K_{oc}	3.14	Russell and McDuffie 1986
	4.17	Sullivan et al. 1982
Vapor pressure at 25 EC	2.01x10^{-5} mmHg	Donovan 1996
	2.7x10^{-5} mm Hg	Staples et al. 1997
Polymerization	No data	
Photolysis	No data	
Henry's law constant at 25 EC	4.5x10^{-6} atm-m^3/mole	Roy 1994
	8.83x10^{-7} atm-m^3/mole	Staples et al. 1997
Autoignition temperature	403 EC	Weiss 1986
Flashpoint	157 EC	NIOSH 1997
Flammability limits at 25 EC	No data	
Incompatibilities	Reacts explosively with liquid chlorine	Bisesi 1994
Conversion factors (25 EC)	11.36 mg/m^3=approximately 1 ppm 1 mg/m^3=0.088 ppm	Bisesi 1994
Explosive limits	Lower explosive limit: 0.5% at 236 EC	NIOSH 1997

HSDB = Hazardous Substance Data Bank; NIOSH = National Institute for Occupational Safety and Health

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Di-*n*-butyl phthalate is a member of a class of compounds called phthalate esters. During the 1980s, there was an increase in the production of phthalate esters with a world-wide production volume of 2 million tons per year (Thuren and Larsson 1990).

Di-*n*-butyl phthalate can be manufactured via the esterification of phthalic acid with *n*-butyl alcohol in the presence of a catalyst such as sulfuric acid or *p*-toluene sulfonic acid (Bisesi 1994; Cadogan and Howick 1996; EPA 1981). This reaction is generally performed at a temperature of 150 EC along with agitation (EPA 1981). Water from this process is either recovered for other operations or treated and discharged as waste water. Di-*n*-butyl phthalate is finally purified by vacuum distillation and/or with activated charcoal. The majority of phthalate esters are produced in Europe with the United States and Asia and Pacific rim countries producing similar amounts each (Cadogan and Howick 1996).

Production volume records for di-*n*-butyl phthalate could only be located combined with the production volume for di-*iso*-butyl phthalate. The production volume of di-*n*-butyl phthalate with di-*iso*-butyl phthalate in the United States from 1979 to 1994 can be found on Table 5-1 (USITC 1980, 1981, 1982, 1983, 1984, 1985, 1986a, 1986b, 1987, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995).

Di-*n*-butyl phthalate is produced at two locations in the United States (SRI 2000). These locations include: Eastman Chemical Company (Kingsport, Tennessee) and Unitex Chemical Corporation (Greensboro, North Carolina).

5.2 IMPORT/EXPORT

Di-*n*-butyl phthalate is imported to the United States from various countries including Japan, Canada, Mexico, Belgium, and Germany (Deyrup 1999). The total amount of di-*n*-butyl phthalate imported in 1997 was 358,600 pounds (162,700 kg), while for 1998, it was 567,600 pounds (257,500 kg). No quantitative data were located on exports of di-*n*-butyl phthalate. Total phthalate ester exports from the United States in 1977, however, was 42,500 kg (93,700 pounds), and di-*n*-butyl phthalate were estimated

Table 5-1. U.S. Production Volumes of Di-*n*-butyl Phthalate[a]

Year	Production volume (x1,000 kg)
1980	8,226
1981	9,029
1982	7,790
1983	9,187
1984	10,964
1985	9,878
1986	10,858
1987	11,440
1988	11,573
1989	9,725
1990	7,917
1991	8,506
1992	6,555
1993	6,662
1994	7,752

Source: USITC 1980, 1981, 1982, 1983, 1984, 1985, 1986a, 1986b, 1987, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995

[a]with di-*iso*-butyl phthalate

to be about 1% of total phthalate production (EPA 1981). On that basis, about 425 kg (937 pounds) of di-*n*-butyl phthalate was probably exported in 1977. More current data could not be located.

5.3 USE

The most important use of di-*n*-butyl phthalate is as a plasticizer (Cadogan and Howick 1992, 1996). Plasticizers are compounds that are added to other substances in order to make them softer and more flexible (Cadogan and Howick 1996). Di-*n*-butyl phthalate appears to be primarily used as a plasticizer in polyvinyl acetate emulsion adhesives (white glues and carpenter's glues, see Pocius 1991); as a solvent for oil-soluble dyes, insecticides, peroxides, and other organics; as an antifoam agent; as a fiber lubricant in the textile industry; as a solvent/plasticizer for nitrocellulose lacquers (Eastman Chemical Company 1999a); and as epoxy resins (EPA 1981, see also Cadogan and Howick 1992, 1996; Towae et al. 1992). Although there was limited use of di-*n*-butyl phthalate in polyvinyl chloride (PVC) plastics during the 1970s and 1980s, it is not currently used as a plasticizer in PVC (NTP 2000). Di-*n*-butyl phthalate is also used as a fragrance fixative (Eastman Chemical Company 1999b; EPA 1981), and as a plasticizer in polysulfides and polyurethanes, and as an alcohol denaturant (EPA 1981). Due to the higher volatility of di-*n*-butyl phthalate compared to other phthalate esters, it is unsuitable as a plasticizer in products that will be exposed to high temperature conditions on a continual basis. It is, however, very suitable in imparting high flexibility, especially at lower temperatures (Cadogan and Howick 1996). Di-*n*-butyl phthalate is often used in conjunction with higher molecular weight esters to improve the flexibility of plasticizer combinations (Cadogan and Howick 1992).

Di-*n*-butyl phthalate has also been used in a number of other applications throughout the world. It has been used in cosmetics, lubricants, floor carpets, tapestry, nail polish (Fishbein 1992), clothing treatments for chiggers (Metcalf 1994), and rubber settings in dentistry (Tesk et al. 1993), for measurement of pore space in carbon black (Dannenberg et al. 1992), and dehydration of maleic acid (Felthouse et al. 1995), as a fuel stabilizer/plasticizer in propellents (Lindner 1993b), in nitroglycerin explosives as a desensitizer (Lindner 1993a), as a solvent for chlorinated rubber, in leather varnishes and lacquers (Bisesi 1994), as an adjusting agent for lead chromate pigments, as a concrete additive to impart work ability, and in polyvinyl acetate emulsions (EPA 1981). Di-*n*-butyl phthalate is listed by EPA as an inert ingredient in some pesticides (EPA 1999a) and an active ingredient in others (EPA 1999b).

A more current break down of usage data for di-*n*-butyl phthalate could not be located. Table 5-2 presents facilities that manufacture or use di-*n*-butyl phthalate according to Toxics Release Inventory (TRI) data.

5.4 DISPOSAL

Currently, a number of different disposal operations may occur for di-*n*-butyl phthalate. During the manufacturing of plasticizers, aerosols containing di-*n*-butyl phthalate can reach concentrations of 500 mg/m^3 (Cadogan and Howick 1996). Many facilities have begun using incineration equipment to reduce aerosol concentrations to practically zero. Also, after transportation or storage operations have ceased, di-*n*-butyl phthalate is generally washed out from its storage containers. This wash water is passed through a series of separators to remove residuals, which are then incinerated.

Some products containing phthalate ester plasticizers (e.g., flooring) may lose plasticizer through extraction by soapy water during cleaning operations (Cadogan and Howick 1996). This waste water could then flow into municipal sewage systems, where it will be later treated and discharged into the environment.

Finally, since di-*n*-butyl phthalate is found in many household products, it may ultimately be disposed of into municipal landfills (Cadogan and Howick 1996).

Table 5-2. Facilities that Produce, Process, or Use Di-n-butyl Phthalate

State[a]	Number of facilities	Range of maximum amounts on site in pounds[b]	Activities and uses[c]
AR	3	100–99,999	9, 10, 13
AZ	1	1,000–9,999	10
CA	7	0–99,999	8, 10, 12, 13
CO	1	10,000–99,999	8
FL	3	100,000–999,999	8, 11
GA	2	1,000–99,999	8, 9
IA	2	10,000–99,999	9, 10
IL	6	0–99,999	8, 9, 10
IN	4	100–99,999	2, 3, 8, 13
KS	2	10000–999,999	8, 10
KY	2	100–99,999	8, 12
LA	1	10,000–99,999	13
MA	4	1,000–999,999	8, 9, 10
MD	1	10,000–99,999	8
MI	3	100–99,999	10, 12, 13
MO	2	1,000–9,999	8, 9
NC	7	100–999,999	1, 4, 8, 10, 11, 12
NE	1	1,000–9,999	8, 9
NJ	7	1,000–99,999	2,3,4,8,10,11, 13
NY	8	1,000–99,999	2,3,8,10,11, 13
OH	3	1,000–99,999	8, 13
OK	1	100,000–999,999	7
PA	3	1,000–99,999	8, 13
RI	1	1,000–9,999	2, 3, 8
TN	3	1,000–999,999	1, 3, 4, 8, 12
TX	4	1,000–999,999	8, 10, 13
UT	1	10,000–99,999	13
VA	2	1,000–999,999	8
WA	2	1,000–99,999	10, 11, 13
WI	2	1,000–9,999	8, 10

Source: TRI99 2001

[a]Post office state abbreviations used
[b]Range represents maximum amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Di-*n*-butyl phthalate has been identified in at least 471 of the 1,585 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2001). However, the number of sites evaluated for di-*n*-butyl phthalate is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 469 are located within the United States and 2 are located in the Commonwealth of Puerto Rico (not shown).

Di-*n*-butyl phthalate is one of several phthalate esters that are widely used as a plasticizers in a range of polymers (e.g., polyvinyl acetate, nitrocellulose) 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 all environmental media. Therefore, humans may be exposed to di-*n*-butyl phthalate by inhalation, by ingestion of water or food containing di-*n*-butyl phthalate, and by dermal contact with plastics, cosmetics, or other materials containing di-*n*-butyl phthalate.

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 transported to water and/or 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; degradation in the presence (aerobic) and absence (anaerobic) of oxygen has been reported. Exposure of the general population to di-*n*-butyl phthalate may occur through contact with contaminated air, water, food, soil, and/or products in which di-*n*-butyl phthalate is intentionally incorporated.

6.2 RELEASES TO THE ENVIRONMENT

The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

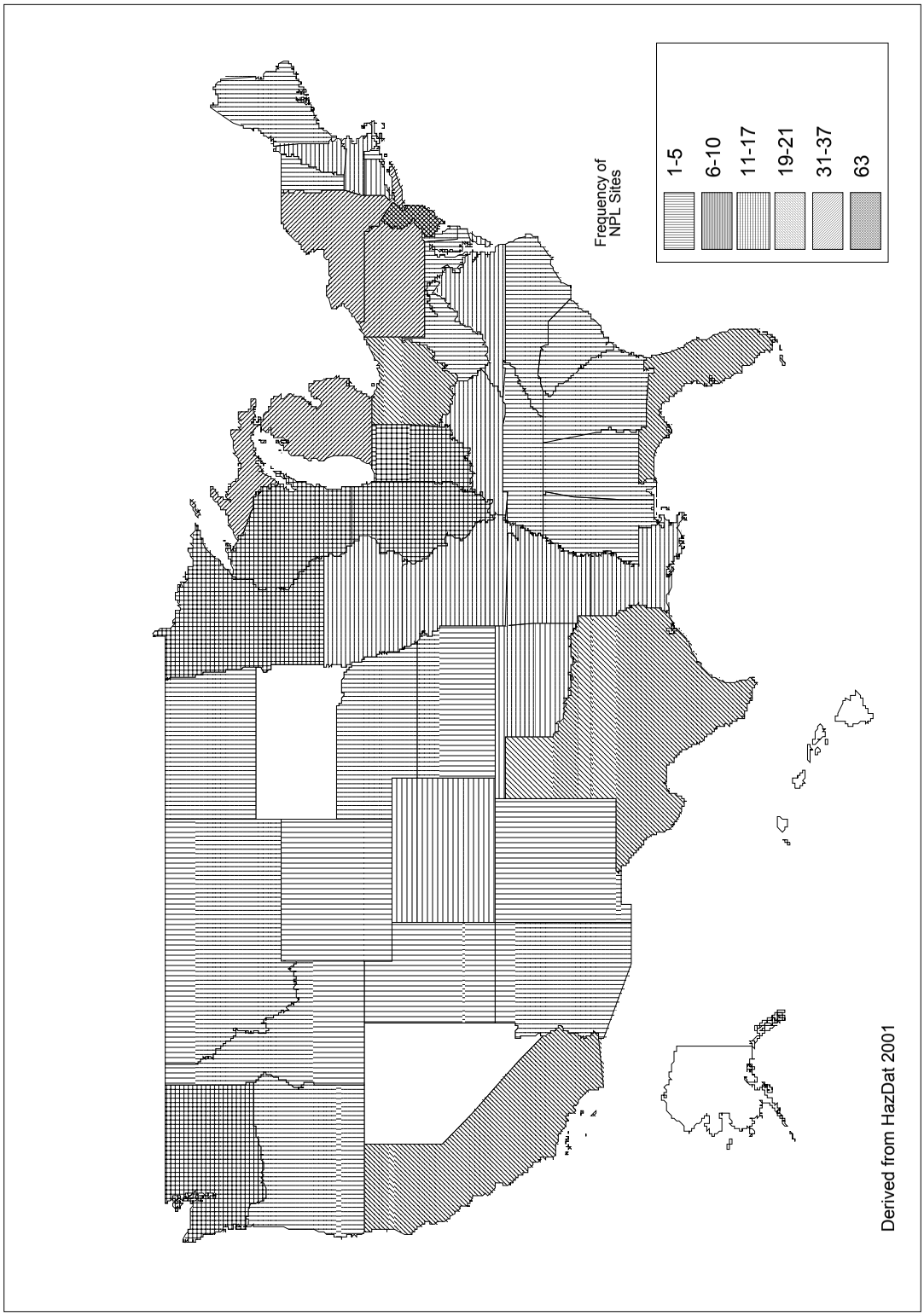


Figure 6-1. Frequency of NPL Sites with Di-n-butyl Phthalate Contamination

Di-*n*-butyl Phthalate has been identified in a variety of environmental media (air, surface water, leachate, groundwater, soil, and sediment) collected at 471 of 1,585 current or former NPL hazardous waste sites (HazDat 2001).

6.2.1 Air

As presented in Chapter 4, di-*n*-butyl phthalate has a relatively low vapor pressure and Henry's law constant, as well as a relatively high octanol/water partition coefficient and soil sorption coefficient. This combination of properties is consistent with a chemical that is found to only a limited extent in air (see Staples et al. 1997). However, di-*n*-butyl phthalate appears to be ubiquitous in air at very low levels (see Section 6.4), apparently from the widespread distribution and use of plastics and other products containing di-*n*-butyl phthalate. In Sweden, Thurén and Larsson (1990) could not correlate di-*n*-butyl phthalate fallout rates with specific sources or transport routes on a nationwide basis. They found no "distributional patterns or gradient," which suggests that any local patterns were obscured by di-*n*-butyl phthalate contribution from other sources or that emission sources of roughly equal magnitude were diffuse. In contrast, monitoring data show that elevated fallout concentrations of bis(2-ethylhexyl) phthalate (a similar molecule) are associated with industrial activity (Thurén and Larsson 1990). Elevated fallout concentrations of bis(2-ethylhexyl) phthalate were only seen near a stack, and no elevated concentrations could be seen 2 km away from the stack. No pattern associating distance from sources and concentration was seen with di-*n*-butyl phthalate by Ritsema et al. (1989) in Lake Yssel in the Netherlands, while for other higher-molecular-weight phthalate esters, a pattern was evident. The authors suggested that atmospheric fallout from diffuse sources may be the dominant mechanism by which di-*n*-butyl phthalate enters the lake.

The possibility of many diffuse sources of di-*n*-butyl phthalate is supported by some of the uses. For example, some of the products that contain di-*n*-butyl phthalate include thin sheets and coatings (including such products as floor wax [Weschler et al. 1990] and paint [Crump 1995]). These products characteristically have large surface area-to-volume ratios, which may allow di-*n*-butyl phthalate to volatilize more readily relative to other products with smaller surface area-to-volume ratios. For example, Crump (1995) reported that 0.04 mg/m^3 of di-*n*-butyl phthalate, which had volatilized from paint, was detected in indoor air. Cadogan and Howick (1996) reported an indoor overall emission rate of 2.3×10^{-4} mg/second-m^3 at 25 EC for all phthalate plasticizers in products such as wall coverings, flooring, upholstery, and wire insulation.

Di-*n*-butyl phthalate is a component of cigarette and wood smoke (Otson et al. 1991) and waste incinerator stacks (Jay and Stieglitz 1995; Nishikawa et al. 1992). Di-*n*-butyl phthalate is listed by EPA as an inert ingredient in some pesticides (EPA 1999a) and an active ingredient in others (EPA 1999b).

Releases to the atmosphere have been reported in EPA Toxic Release Inventory (TRI99 2001), and the quantities are presented in Table 6-1. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list. Nonetheless, according to TRI99 (2001), manufacturing and processing facilities in 32 states emitted an estimated 36,477 pounds (*ca.* 17 metric tons) to the air, or approximately 9% of the total environmental release.

Di-*n*-butyl phthalate has also been identified in the condensed water (Jay and Stieglitz 1995) and exhaust gas (Nishikawa et al. 1992) from waste incinerators. In addition, Jones et al. (1996) used the CORAL+ model to estimate that a large U.S. city would emit approximately 200 g/year from all manholes, based on sewage concentrations of 7 µg di-*n*-butyl phthalate/L of sewage. The model was very sensitive to manhole ventilation rates and the authors noted that the estimate was probably very conservative. Di-*n*-butyl phthalate has been identified in 2 air samples collected from the 471 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2001).

6.2.2 Water

Bauer and Herrmann (1997) reported the concentration of di-*n*-butyl phthalate in the leachate from various fractions of household wastes from the regions of Bayreuth and Straubling in Germany. The wastes included food waste, paper for recycling, unusable paper, cardboard, plastic films, other plastics, textiles, 8–40 mm screened fraction, <8 mm screened fraction, compound packing waste, compound materials, and disposable diapers. It is anticipated that household waste from continental Europe is similar to that in the United States, so the same profile would be expected in both places. Further information on this study is presented in Section 6.4.

According to TRI99 (2001), releases to water amount to approximately 279 pounds (0.13 metric tons) or approximately 0.07% of the total amount released to all compartments (see Table 6-1). Releases to underground injection wells amount to approximately 290,000 pounds (132 metric tons) or approximately 74% of the total amount released to all compartments. These releases occurred only in the

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Di-n-butyl Phthalate

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on- and off-site release
AL	1	No data	No data	No data	No data	No data	No data	No data
AZ	1	192	No data	No data	No data	192	No data	192
AR	4	751	0	No data	No data	751	No data	751
CA	14	568	0	No data	No data	568	1,324	1,892
CO	2	0	0	No data	No data	0	No data	0
FL	4	910	0	290,000	No data	290,910	250	291,160
GA	5	575	No data	No data	No data	575	No data	575
IL	16	4,070	0	No data	No data	4,070	20,722	24,792
IN	6	34	No data	No data	No data	34	1,127	1,161
IA	4	1	No data	No data	No data	1	171	172
KS	2	2,360	No data	No data	No data	2,360	2,069	4,429
KY	2	0	No data	No data	No data	0	No data	0
LA	2	0	0	No data	No data	0	No data	0
MD	1	0	No data	No data	No data	0	No data	0
MA	8	251	No data	No data	No data	251	No data	251
MI	6	43	0	No data	9,421	9,464	9,718	19,182
MN	2	No data	No data	No data	No data	No data	No data	No data
MO	6	501	No data	No data	No data	501	318	819
NE	1	10	No data	No data	No data	10	1,014	1,024
NJ	18	415	0	No data	0	415	4	419
NY	10	267	92	No data	0	359	1,031	1,390
NC	12	3,862	0	No data	4,224	8,086	8,662	16,748
OH	13	22	1	No data	No data	23	1,390	1,413
OK	2	5	No data	No data	No data	5	No data	5
PA	6	260	No data	No data	No data	260	No data	260

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Di-n-butyl Phthalate (*continued*)

		Reported amounts released in pounds per year[a]						
State[b]	Number of facilities	Air[c]	Water	Underground injection	Land	Total on-site release[d]	Total off-site release[e]	Total on- and off-site release
RI	1	365	No data	No data	No data	365	1,800	2,165
TN	4	14,211	160	No data	No data	14,371	No data	14,371
TX	14	436	0	No data	0	436	No data	436
UT	1	13	No data	No data	No data	13	No data	13
VA	5	851	21	No data	No data	872	No data	872
WA	2	5,498	5	No data	0	5,503	250	5,753
WI	5	6	No data	No data	No data	6	500	506
Total	184	36,477	279	290,000	13,645	340,401	50,350	390,751

Source: TRI99 2001

[a]Data in TRI are maximum amounts released by each facility.
[b]Post office state abbreviations are used.
[c]The sum of fugitive and stack releases are included in releases to air by a given facility.
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[e]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

state of Florida. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list. Di-*n*-butyl phthalate has been identified in 217 groundwater and 78 surface water samples collected form the 471 NPL hazardous waste sites, where it was detected in some environmental media (HazDat 2001).

Di-*n*-butyl phthalate may also be released into surface waters from industrial sources (Sheldon and Hites 1979), municipal waste water (Stubin et al. 1996), and leachate from sanitary landfills (EPA 1990a; Kinman et al. 1995). Di-*n*-butyl phthalate has also been reportedly released to groundwater from a hazardous waste site (Eckel et al. 1993).

Di-*n*-butyl phthalate has been detected in 5% of the urban runoff samples from 2 of the 19 cities tested by EPA (Howard 1989). Concentrations in this urban waste water ranged from 0.5 to 11 µg/L. Sewage sludge has been shown to concentrate di-*n*-butyl phthalate from water by about 25-fold. A concentration of 966 µg/L sludge was reported by Feiler et al. (1980). It is believed that di-*n*-butyl phthalate in waste water comes from a variety of sources including wash water used on vinyl flooring (Cadogan and Howick 1996). Disposal of secondary sewage effluent by rapid infiltration into the subsurface has been reported to produce a plume over 3,500 m long of groundwater contaminated with di-*n*-butyl phthalate at concentrations up to 450 mg/L (Barber 1992; Barber et al. 1988). 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).

6.2.3 Soil

According to TRI99 (2001), releases to land amount to approximately 13,645 pounds (6.2 metric tons) or approximately 3.5% of the total (see Table 6-1). Based on this analysis of TRI data alone, soil does not appear to be a medium that commonly receives industrial releases. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list. Di-*n*-butyl phthalate has been identified in 280 soil and 126 sediment samples collected from the 471 NPL hazardous waste sited where it was detected in some environmental media (HazDat 2001).

No other release of di-*n*-butyl phthalate to soils has been reported; however, di-*n*-butyl phthalate has been reported in leachate from sanitary landfills (EPA 1990a; Kinman et al. 1995) and in groundwater from a hazardous waste site (Eckel et al. 1993). These monitoring data indicate release to soil. Thurén and

Larsson (1990) also noted that the average yearly atmospheric input to soil in Sweden was 202 µg/m^2 for di-*n*-butyl phthalate. Also, di-*n*-butyl phthalate may seep into soil from di-*n*-butyl phthalate containing sewage sludge that is deposited on land.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Di-*n*-butyl phthalate appears to be ubiquitous in air at low levels, is in both the vapor phase and associated with particulates, and is subject to both wet (rain and snow) and dry (wind and settling) deposition on the Earth's surface. Eisenreich et al. (1981) calculated that wet and dry deposition of di-*n*-butyl phthalate into the five Great Lakes amounted to 47.7 metric tons per year, which corresponds to an average fallout rate of 16.2 µg/m^2 per month. Thurén and Larsson (1990) reported that the average fallout rate in Sweden for di-*n*-butyl phthalate was 16.8 µg/m^2 per month (the range was 1.98–335.5 µg/m^2 per month). Thurén and Larsson (1990) also estimated the median fallout concentration to be 36 ng/L. The authors also noted that for a related phthalate ester, bis(2-ethylhexyl) phthalate, fallout rate decreased with increasing distance (but only up to 2 km away) from a stack at a facility that used bis(2-ethylhexyl) phthalate (see Section 6.2). A similar behavior is likely for di-*n*-butyl phthalate. Nonetheless, the authors noted that no specific overall fallout patterns were observed. This is consistent with a diffuse source of di-*n*-butyl phthalate in the atmosphere. In addition, di-*n*-butyl phthalate has been found in 2 m deep Antarctic snow (Desideri et al. 1994) and in the snow in the Austrian Alps (Gröllert et al. 1997), suggesting that di-*n*-butyl phthalate can be transported for long distances so that di-*n*-butyl phthalate measured in one part of the world may have originated elsewhere. This transport is likely particle sorbed di-*n*-butyl phthalate because vapor phase di-*n*-butyl phthalate reacts rapidly with hydroxyl radicals in the atmosphere (see Section 6.3.2.1), while the particle-sorbed chemical does not react rapidly with hydroxyl radicals (di-*n*-butyl phthalate is associated with particulates at low temperatures). Atmospheric fallout is negatively correlated with temperature so that less di-*n*-butyl phthalate is subject to fallout in the summer than in the winter (Staples et al. 1997; Thurén and Larsson 1990). This is in keeping with a higher proportion of the atmospheric di-*n*-butyl phthalate in the vapor state in the warm summer and less in the cold winter.

In water, di-*n*-butyl phthalate adsorbs to suspended particles, but, in many cases, the majority remains dissolved. Based on log K_{oc} values of 3.14 (Russell and McDuffie 1986) and 4.17 (Sullivan et al. 1982),

di-*n*-butyl phthalate is anticipated to sorb relatively strongly to suspended particulates and sediments (see Swann et al. 1983); however, this is not always observed. Dissolved di-*n*-butyl phthalate is more readily advected and may be more available for biodegradation than particle-bound material. When dissolved in water, di-*n*-butyl phthalate may be associated with dissolved humic materials, potentially increasing the apparent water solubility by a small amount. Based on Henry's law constants of $4.5x10^{-6}$ (Roy 1994) and $8.83x10^{-7}$ (Staples et al. 1997) atm-m^3/mole, di-*n*-butyl phthalate is not expected to volatilize significantly from water to the atmosphere (Lyman 1982). Germain and Langlois (1988) and Staples et al. (1997) reported that 83.5–86% of the di-*n*-butyl phthalate was dissolved and 14–16.5% was bound to suspended material (the concentrations of suspended material were 3.0–7.83 mg/L) in Niagara and St. Lawrence Rivers. By contrast, Ritsema et al. (1989) reported that 29–57% of the di-*n*-butyl phthalate in Lake Yssel water (the Netherlands) was dissolved, while 43–71% was associated with suspended material. Matsuda and Schnitzer (1971) reported that di-*n*-butyl phthalate was slightly more soluble in water containing fulvic acids extracted from soil than in pure water, and that solubility increased with increasing fulvic acid concentration. Therefore, di-*n*-butyl phthalate may be present in higher dissolved concentrations in waters with high concentrations of humic materials than in waters with low concentrations of humic materials. Finally, in an estuary in the United Kingdom, Preston and Al-Omran (1986, 1989) and Al-Omran and Preston (1987) reported that 66–86% of the di-*n*-butyl phthalate was dissolved, while 14–34% was bound to suspended material, and that more adsorption occurs at higher salt concentration. The authors reported that suspended material averaged 1,524 mg/L.

No reports were located that detailed the sorption of di-*n*-butyl phthalate specifically to freshwater sediments; however, it is anticipated that the sorption to these sediments will be similar to that of suspended materials. Sullivan et al. (1982) reported that di-*n*-butyl phthalate is rapidly adsorbed from seawater onto marine sediment, but they did not report a K_{oc} so that comparison with other reports is difficult.

In soil, di-*n*-butyl phthalate is expected to have limited mobility based on its log K_{oc} (see Table 4-2). However, some migration to groundwater occurs, but may be limited to soils with low organic content soils or sites with high water tables. Russell and McDuffie (1986) reported a log K_{oc} of 3.14 in a soil in Broome County, New York. According to Swann et al. (1983), this K_{oc} is indicative of relatively low mobility, suggesting that di-*n*-butyl phthalate will have limited migration to groundwater. Nonetheless, Eckel et al. (1993) reported finding di-*n*-butyl phthalate in the groundwater under the Hipps Road landfill NPL site in Florida. This site was developed at a location with unconsolidated medium- to fine-grained

sand that allowed rapid movement of percolating water. Similarly, Barber (1992) reported finding di-*n*-butyl phthalate in the groundwater near rapid infiltration beds where secondary sewage effluent was disposed for over 50 years, and Kinman et al. (1995) reported the presence of di-*n*-butyl phthalate in sanitary landfill leachate.

In addition to the cases noted above, the presence of organic solvents in hazardous waste sites may increase the solubility of 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 six times its normal water solubility (Nyssen et al. 1987).

Finally, data indicate that di-*n*-butyl phthalate can partition from food and water into a variety of organisms. Studies using radioactively labeled di-*n*-butyl phthalate have shown accumulation of radioactivity in aquatic invertebrates (Sanders et al. 1973) and fish (Wofford et al. 1981). Most of the accumulated radioactivity is apparently in the form of the primary metabolite, mono-*n*-butyl phthalate (Howard 1989). Numerous experiments have shown that the accumulation of di-*n*-butyl phthalate in the aquatic and terrestrial food chain is limited by biotransformation (i.e., transformation of chemical compounds within a living system), which progressively increases with trophic level (Staples et al. 1997). In general, bioconcentration factors decrease for organisms that possess more advanced metabolic systems (Stalling et al. 1973). For example, the mean bioconcentration factors for algae, crustaceans, insects, and fish are 3,399, 662±229, 624±144, and 167 mg/g (wet weight), respectively (Staples et al. 1997).

In greenhouse studies, Shea et al. (1982) demonstrated dose-dependent partitioning of di-*n*-butyl phthalate from soils into corn, soybean, and wheat seedlings. For example, plant to soil bioconcentration factors (defined as the ratio of wet weight concentrations in plant and soil, respectively) were <0.002 for corn, indicating the limited bioaccumulation potential of di-*n*-butyl phthalate by terrestrial plants.

6.3.2 Transformation and Degradation

It should be noted that many of the studies reporting di-*n*-butyl phthalate biodegradation use radiolabeled material as the substrate and measure $^{14}CO_2$ as an indication of the extent of biodegradation. The reported percentage of evolved $^{14}CO_2$ indicates the amount of mineralization, but is not necessarily an indication of

the extent of degradation. In addition to oxidation to CO_2, microbial communities can also, for example, incorporate organic substrates into cellular materials, or produce simple degradation products or high molecular-weight materials. All of these processes contribute to the overall removal of the substrate, but are not indicated by the percentage of $^{14}CO_2$ reported.

6.3.2.1 Air

In air, di-*n*-butyl phthalate in vapor form would be expected to react with hydroxyl radicals since it has extractable hydrogens. An overall hydroxyl radical reaction rate of 9.28×10^{-12} cm^3/molecule-second was calculated using the AOPWin program (version 1.88, Meylan and Howard 1993). Assuming 1.5×10^6 •OH molecules/cm^3, the half-life of di-*n*-butyl phthalate vapor in air can be calculated to be approximately 14 daylight hours. For di-*n*-butyl phthalate adsorbed to airborne particles, the half-life may be considerably longer and may account for the long range transport of di-*n*-butyl phthalate, but this has not been studied.

6.3.2.2 Water

Many papers describing the biodegradation of di-*n*-butyl phthalate in environmental waters and waste water are available in the literature (Scholz et al. 1997; Staples et al. 1997). Di-*n*-butyl phthalate is frequently reported to degrade 50–100% aerobically within 1–28 days in both fresh and marine water, and anaerobically over 90% within 30 days in fresh water (Staples et al. 1997). In a river die-away test using water from three rivers in the Netherlands, Schouten et al. (1979) reported that 90% of the initial 50 µg/L di-*n*-butyl phthalate was removed in 3 days, while only 10% was lost in the sterile controls. Johnson et al. (1984) found that di-*n*-butyl phthalate was degraded aerobically in water and sediment from Little Dixie Lake in Columbia, Missouri. Approximately 63% degradation was observed in 7 days and 70% degradation was observed in 14 days as measured by $^{14}CO_2$ evolution using initial di-*n*-butyl phthalate concentrations of 0.082–8.2 mg/L. In fresh and estuarine waters from U.S. sources, EPA (1984a) reported that the range of time for one-half of the initial di-*n*-butyl phthalate (500 µg/L) to disappear was 1.7–13 days. The authors reported a 0–7 day lag period, and no degradation was seen in sterile controls. Johnson and Lulves (1975) reported that di-*n*-butyl phthalate (initial concentration of 1 mg/L) incubated anaerobically in sediment degraded 61% in 7 days and 98% in 30 days as measured by recovery of di-*n*-butyl phthalate.

In contrast to biodegradation, abiotic hydrolysis appears to be a slow process. EPA (1989d) reported that the hydrolysis half-life for di-*n*-butyl phthalate was approximately 22 years.

In screening tests using activated sludge, removal of >90% of the initial di-*n*-butyl phthalate is reported. For example, Kodama and Takai (1974) reported that 97–99.5% of the di-*n*-butyl phthalate at 0.1–1.0 mg/L degraded in a 3-day test. Using acclimated sludge in a semi-continuous activated sludge test, O'Grady et al. (1985) reported that >90% of the initial of 3 mg/L concentration of di-*n*-butyl phthalate degraded in 1 day. Under anaerobic conditions in activated sludge, di-*n*-butyl phthalate was completely degraded to carbon dioxide and methane over a period of 20 days (Hannah et al. 1986). Shelton and Tiedje (1984) reported that 75–100% of the theoretical yield of methane was evolved in 56 days.

6.3.2.3 Sediment and Soil

Di-*n*-butyl phthalate also rapidly degrades in soil and sediments (Staples et al. 1997). For example, 500 µg/L of di-*n*-butyl phthalate in river and estuarine sediment samples degraded to one-half the initial concentration in 1–5 days (EPA 1984a), and 92% (by $^{14}CO_2$ evolution) of the di-*n*-butyl phthalate was degraded in lake sediment in 14 days at 28 EC (Johnson et al. 1984). Inman et al. (1984) reported that 1 mg/L di-*n*-butyl phthalate in four soils was degraded to >80% (determined by $^{14}CO_2$ evolution) within 80 days in almost every case. Silica sand and a sterile control showed almost no degradation. One of the soils, Plainfield, required 200 days to reach 89.6% $^{14}CO_2$ evolution. In four samples of Little Popo Agie River (Wyoming) sediment, Heitkamp and Johnson (1984) reported that di-*n*-butyl phthalate, at a concentration of 25.6 µg/L, was degraded aerobically to 71–75% (measured by $^{14}CO_2$ evolution) in 14 days. In one sample, degradation was reported to be only 2.2%. Samples were taken from both up- and downstream of an oil field waste water discharge point; the sediment that degraded only 2.2% of the initial di-*n*-butyl phthalate was taken at the discharge point, which suggests that toxic substances may have retarded the degradation.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

As presented in Chapter 4, di-*n*-butyl phthalate has a relatively low vapor pressure and Henry's law constant, as well as a relatively high octanol/water partition coefficient and soil sorption coefficient. This combination of properties is consistent with a chemical that is found to only a limited extent in air. Nonetheless, di-*n*-butyl phthalate appears to be widespread in air at low levels, with urban air having somewhat higher concentrations than air in rural or uninhabited areas. It should be noted that because phthalates are widespread, they appear in the laboratory environment, and considerable effort must be exercised by analysts to ensure that external contamination has not influenced the results. The monitoring studies reported here appear to have taken reasonable efforts to eliminate contamination from their analyses. Di-*n*-butyl phthalate has been reported over the Pacific and Atlantic Oceans at levels of approximately $1x10^{-6}$ mg/m^3 (1 ng/m^3) (Atlas and Giam 1981; Giam et al. 1980), in outdoor air in Sweden, the United States (Thurén and Larsson 1990), and Canada (Otson et al. 1991) at $2.3x10^{-7}$–$4.99x10^{-5}$ mg/m^3 (0.23–49.9 ng/m^3), over New York City at levels of $3.3x10^{-6}$–$5.7x10^{-6}$ mg/m^3 (3.3–5.7 ng/m^3) (Bove et al. 1978), in industrialized areas along the Niagara River at levels of $4.5x10^{-6}$ mg/m^3 (4.5 ng/m^3) as vapor and at $6.2x10^{-6}$ mg/m^3 (6.2 ng/m^3) in particulate matter (Hoff and Chan 1987), in indoor air in a "sick" building at levels of $1.2x10^{-3}$–$5.9x10^{-3}$ µg/m^3 (1,200–5,900 ng/m^3) (but not in the air on the roof of the building) (Weschler et al. 1990), in residences in Canada at >$1.0x10^{-5}$ mg/m^3 (>10 ng/m^3) (Otson et al. 1991), cigarette and wood smoke (Otson et al. 1991), and waste incinerator stacks at $7.7x10^{-3}$ mg/m^3 (7,700 ng/m^3) (Jay and Stieglitz 1995; Nishikawa et al. 1992). Crump (1995) reported that 0.04 mg/m^3 of di-*n*-butyl phthalate from paint was detected in indoor air. As noted in Section 6.2.1, Cadogan and Howick (1996) reported that an indoor overall emission rate of $2.3x10^{-4}$ mg/second-m^3 at 25 EC has been calculated for all phthalate plasticizers in products such as wall coverings, flooring, upholstery, and wire insulation.

6.4.2 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. The National Drinking Water Contaminant Occurrence Database (NDOD), which contains data from ambient water samples, lists the number of detections of di-*n*-butyl phthalate in groundwater and surface water at several locations

around the United States. Di-*n*-butyl phthalate was detected in groundwater at 1 of 363 sites (0.3% of sites) with a concentration of 57 µg/L (EPA 2000a). In lakes/reservoirs, di-*n*-butyl phthalate was detected at 2 of 15 sites (13.3% of sites) with a range and average concentration of 2.5–10.7 and 6.6 µg/L, respectively (EPA 2000a). In other surface waters, di-*n*-butyl phthalate was detected at 9 of 253 sites (3.6% of sites) with a range and average concentration of 0.2–150 and 17.1 µg/L, respectively (EPA 2000a). 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 the distribution of di-*n*-butyl phthalate. This observation is consistent with the continuous extensive wet and dry deposition from air (see Section 6.3.1). 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); lower average concentrations were noted downstream (range, 0.1–10.4 µg/L). The difference between upstream and downstream average concentrations was not large and may reflect analytical variability. 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 0.5–0.7 µg/L (McFall et al. 1985b).

The results of a 10-city drinking water survey reported 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 five cities; the level was 5.0 µg/L for one city (Keith et al. 1976).

Bauer and Herrmann (1997) reported that di-*n*-butyl phthalate was present in the leachate from various fractions of household wastes from the regions of Bayreuth and Straubling in Germany. The wastes included food waste, paper for recycling, unusable paper, cardboard, plastic films, other plastics, textiles, 8–40 mm screened fraction, <8 mm screened fraction, compound packing waste, compound materials, and disposable diapers. Leachate from a mixture of all waste categories except food waste contained a maximum of 34 µg/L of di-*n*-butyl phthalate, while leachate from a mixture of waste categories limited to plastic films, other plastics, textiles, 8–40 mm screened fraction, <8 mm screened fraction, and compound materials contained a maximum of 63 µg/kg di-*n*-butyl phthalate. The authors were careful to exclude inadvertent sources of phthalate esters. This report indicates that di-*n*-butyl phthalate is present in European household waste and that it leaches from that waste to percolating water. The extent to which

this occurs in a landfill is unclear as is whether or not the dissolved di-*n*-butyl phthalate leaches to groundwater after leaving landfills.

6.4.3 Sediment and Soil

Considerable variability is encountered in the available data on sediments and soils. 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 15–93 µg/kg dry weight of di-*n*-butyl phthalate (Murray et al. 1981). Bauer and Herrmann (1997) reported that di-*n*-butyl phthalate was present in household waste in Europe (see Sections 6.4.2 and 6.4.4) and leached from waste. It is anticipated that this leaching will occur in a municipal waste landfill and that di-*n*-butyl phthalate will enter the soil surrounding these landfills. It is further anticipated that this European waste is not considerably different from waste generated in the United States.

6.4.4 Other Environmental Media

Very little recent information on di-*n*-butyl phthalate concentrations in other environmental media in the United States is available. Recent information, however, is available for some European countries and for Canada, and these studies show the presence of di-*n*-butyl phthalate in a range of foods and textiles. It should be noted that di-*n*-butyl phthalate is approved by the U.S. Food and Drug Administration (FDA) for use as an indirect food additive in adhesives (21 CFR 175.105), in paper and paperboard in contact with aqueous and fatty foods (21 CFR 176.170), in cellophane (not to exceed 5%) (21 CFR 177.1200), and in rubber articles intended for multiple use (21 CFR 177.2600), and thus, di-*n*-butyl phthalate may enter food products indirectly in the United States. Some of the European studies show migration from adhesives into foodstuffs. In addition, di-*n*-butyl phthalate is used as a lubricant in the manufacture of textiles and has been found in clothing in Europe. Mean concentrations of di-*n*-butyl phthalate in food group samples, from 1993 Total Diet Study conducted by the Ministry of Agriculture, Fisheries & Food (MAFF) in Great Britain, were 0.003, 0.09, 0.1, and 0.2 µg/g (wet weight) for milk, carcass meat, eggs, and poultry, respectively (MAFF 1996a). In a market basket survey of 98 different food types obtained from Halifax, Canada in 1986, di-*n*-butyl phthalate was detected in butter (1.5 µg/g), freshwater fish

(0.5 µg/g), cereal products (ranged from not detected up to 0.62 µg/g), baked potatoes (0.63 µg/g), coleslaw (0.11 µg/g), bananas (0.12 µg/g), blueberries (0.09 µg/g), pineapples (0.05 µg/g), margarine (0.64 µg/g), white sugar (0.2 µg/g), and gelatin dessert (0.09 µg/g) (Health Canada 1994). In Germany, the concentration of di-*n*-butyl phthalate in milk and milk products ranged from not detected (i.e., <0.01 mg/kg) to 0.07 mg/kg (Bruns-Weller and Pfordt 2000a, 2000b). The authors noted that di-*n*-butyl phthalate concentrations in milk purchased at the retail level were no higher than raw milk. The concentration of di-*n*-butyl phthalate in retail infant formula from Great Britain ranged from <0.05 to 0.09 µg/g (dry weight basis) (MAFF 1998). In Germany, levels of di-*n*-butyl phthalate in baby food ranged from not detected (i.e., <0.01 mg/kg) to 0.03 mg/kg (Bruns-Weller and Pfordt 2000a, 2000b).

Di-*n*-butyl phthalate may enter food materials by uptake from the environment. For example, reported concentrations of di-*n*-butyl phthalate in fish ranged from 78 to 200 µg/kg (Giam and Wong 1987; Stalling et al. 1973; Williams 1973). Concentrations of di-*n*-butyl phthalate in fish from various Great Lakes (United States) harbors and tributary mouths ranged from $<2x10^{-5}$ to $3.5x10^{-2}$ µg/kg wet weight (de Vault 1985). Oyster and clam concentrations of di-*n*-butyl phthalate ranged from 40 to 570 µg/kg (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 of di-*n*-butyl phthalate ranged from 50 to 150 µg/kg.

Table 6-2 summarizes the concentration of di-*n*-butyl phthalate found in food packaged in paper and board packing materials (range, <0.02–62 µg/g food), and the concentration of di-*n*-butyl phthalate in the packaging materials used to contain the foods (range, <5–5,860 µg/g packaging material) (MAFF 1995). In another study, Aurela et al. (1999) found that di-*n*-butyl phthalate could migrate into sugar from adhesives used in the joints of paper packaging materials. After storage in a package for 4 months, the sugar contained 0.5–1.0 mg/kg of di-*n*-butyl phthalate; unpackaged sugar did not contain any phthalates. Higher concentrations were reported for that portion of the sugar that touched the seams of the packaging material. Di-*n*-butyl phthalate found in coffee filter paper may contaminate coffee beverages during the brewing process. For example, two of nine samples of coffee filters contained 8,200 and 15,000 µg/kg di-*n*-butyl phthalate (Fricker and Hardy 1990).

Table 6-3 summarizes the concentration of di-*n*-butyl phthalate detected in various categories of waste from European sources (Bauer and Hermann 1997). The authors also calculated that 11.4–106.7 mg/kg di-*n*-butyl phthalate was present in the waste on a dry-weight basis and constituted the second most

Table 6-2. Concentration of Di-*n*-butyl Phthalate in Paper and Board Packaging and Food Packaged in Paper and Board

Food types	Number of samples	Concentration in packaging (mg/kg)[a]	Number of samples	Concentration in food (mg/kg)[b]
Bakery products[c] and snacks	20	<5–2,560	5	<0.02–0.9
Confectionery	17	20–550	7	<0.02–5.8
Meat and fish products	7	40–1,380	2	0.05, 4.4
Fats	21	20–2,500	5	outer, 1.5–8.4 core, 1.4–8.7
Pasta and cereals	11	16–110	2	<0.02, 0.5
Dried fruits	2	10–16	1	<0.02
Flour and sugar	9	<5–450	2	0.2, 1.6
Gravy granules and parmesan cheese[d]	7	150–3,160	5	0.8–62
Miscellaneous	6[e]	29–5,860	2[f]	0.04, 10

Source: MAFF (1995)

[a]Limit of detection was 5 mg/kg packaging.
[b]Limit of detection was 0.02 mg/kg food.
[c]"Backey products" in original source.
[d]These products have been grouped together as they have the same type of packaging.
[e]This group consists of samples of short crust pastry mix, Yorkshire pudding, an ice lolly, waffles, eggs, and vegetable burger mix.
[f]This group consists of one sample of an ice lolly and vegetable burger mix.

Table 6-3. Concentration of Di-*n*-butyl Phthalate in Categories of Household Waste

	Concentration of di-*n*-butyl phthalate (mg/kg)[a,b]		
Waste fraction	Minimum	Maximum	Mean
Food waste	1.8	10.2	5.6
8–40 mm fraction	5.1	67.1	38.1
<8 mm fraction	10.3	17.6	15.0
Paper for recycling	9.6	22.0	15.2
Unusable paper	6.8	22.3	11.6
Cardboard	14.4	121.7	45.6
Plastic films	13.5	105.0	36.2
Other plastics	36.1	762.6	181.2
Textiles	6.0	18.9	10.9
Compound packing waste	60.1	115.3	82.4
Compound materials	609.7	2,160.0	1,473.0
Disposable diapers[c]	3.2	43.0	11.0

Source: Bauer and Herrmann (1997)

[a]Results are from six extractions except “compound materials”, for which the results are for nine extractions.
[b]The listing of the precision of the values presented in this table is the same as the original paper.
[c]Described as “nappies” in the original paper.

commonly found phthalate ester, constituting 6.0–6.7% of the total phthalates found in the waste (bis-2-ethylhexyl phthalate was the most common phthalate ester, constituting 91.9–93.3% of the total phthalates found).

Bruns-Weller and Pfordt (2000b) reported that a variety of clothing sampled in Germany contained levels of di-*n*-butyl phthalate ranging from 0.66 to 30.43 mg/kg. Di-n-butyl phthalate is used as a lubricant for textiles (see Section 5.3).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Di-*n*-butyl phthalate is present in both urban and rural air (1–6 ng/m^3), some drinking waters (0.1–0.5 µg/L; the data are >20 years old), and some foods (3–1,500 µg/kg) (see above). Thus, the general population is likely to be exposed to di-*n*-butyl phthalate at levels that are generally in the low ppb range or below. It should be noted that some of the U.S. data presented above are 10 or more years old, so current exposure levels might be different. Based on these data, the highest exposure to di-*n*-butyl phthalate is most likely to come from some dairy products, fish, and seafood, if these foods comprise a large part of the diet. Di-*n*-butyl phthalate is also an indirect food additive that is present in food containers and may be transferred to foods. There is evidence of this in European and Canadian studies, but not in U.S. studies. It may be more likely that, for the general population, air is the main source of di-*n*-butyl phthalate exposure if dairy products and seafood are not important in the diet. No data were available that could be used to estimate doses from dermal exposure to di-*n*-butyl phthalate.

Chan and Meek (1994) estimated the daily intake of di-*n*-butyl phthalate by the population of Canada (see Table 6-4). Based on the medium-specific intakes, it is estimated that the average daily intake of di-*n*-butyl phthalate for the various age groups in the general population in Canada range from 1.9 to 5.0 µg/kg body weight/day. It should be noted that these estimates do not include intake from consumer products (e.g., nail polish). Based on the percentage of di-*n*-butyl phthalate in some cosmetics (from 0.1 to between 10 and 25%), these products could contribute significantly to the exposure of some members of the general population.

The National Institute for Occupational Safety and Health (NIOSH) conducted the National Occupational Exposure Survey (NOES) from 1981 to 1983 (NIOSH 1988a). Data from the survey show that an estimated 31,502 facilities use di-*n*-butyl phthalate in 199 industries involving 138 occupations (RTECS

Table 6-4. Estimated Daily Intake of Di-*n*-butyl Phthalate by the Population of Canada

Substrate/ medium[a]	Estimated intake by age groups of di-*n*-butyl phthalate (µg/kg body weight/day)				
	0–0.5 years[b]	0.5–4 years[c]	5–11 years[d]	5–19 years[e]	20–70 years[f]
Ambient air	0.00021–0.00030	0.00033–0.00040	0.00033–0.00041	0.00028–0.00038	0.00025–0.00034
Indoor air	0.68	0.91	1.1	0.87	0.78
Drinking water	0.11	0.062	0.033	0.022	0.021
Food	1.6	4.1	3.2	1.4	1.1
Soil	<0.0005–0.0070	<0.00038–0.0054	<0.00013–0.00049	<0.000035–0.00049	<0.000028–0.00040
Total estimated intake	2.4	5.0	2.3	2.3	1.9

Source: Chan and Meek 1994

[a]Mean concentrations in ambient air based on a small study in a limited region of Ontario were 4.5–6.2 ng/m^3; the maximum concentration in indoor air was 2.85 µg/m^3 based on a small and possibly unrepresentative number (n=9) of homes in Montreal; mean values were not specified. It is assumed that people generally spend 4 hours outdoors and 20 hours indoors. Di-*n*-butyl phthalate was not detected in drinking water in a regional study in Ontario (limit of detection, 1.0 µg/L); mean values in surface water and groundwater supplies in Alberta were 1.0 µg/L. Di-*n*-butyl phthalate was detected in butter (1.5 µ/g), fresh water fish (0.5 µg/g), cereal products (ranged from not detected up to 0.62 µg/g), baked potatoes (0.63 µg/g), coleslaw (0.11 µg/g), bananas (0.12 µg/g), blueberries (0.09 µg/g), and pineapples (0.05 µg/g), margarine (0.64 µg/g), white sugar (0.2 µg/g), and gelatin dessert (0.09 µg/g). The detection limits, which were not specified for individual foodstuffs, varied depending on the reagent blank values, interferences arising from coextracted food components, and the fat content of the food (range, 0.01–0.5 µg/g); the content in food stuffs in which di-*n*-butyl phthalate was not detected was considered to be 0. Calculated intakes are based upon consumptions of individual food composites for each age group in the population. The di-*n*-butyl phthalate content in the soil in urban areas of Port Credit, Oakville, and Burlington, Ontario, ranged from <0.1 to 1.4 µg/g. Available data were insufficient to estimate intake from consumer products, though cosmetics may contribute significantly to the exposure of some members of the general population in certain age groups, based on the percentage content of some products (0.1 to between 10 and 25%).
[b]Assumed to weigh 7 kg, breathe 2 m^3 air, drink 0.75 L water, and ingest 35 mg soil.
[c]Assumed to weigh 13 kg, breathe 5 m^3 air, drink 0.8 L water, and ingest 50 mg soil.
[d]Assumed to weigh 27 kg, breathe 12 m^3 air, drink 0.9 L water, and ingest 35 mg soil.
[e]Assumed to weigh 57 kg, breathe 21 m^3 air, drink 1.3 L water, and ingest 20 mg soil.
[f]Assumed to weigh 70 kg, breathe 23 m^3 air, drink 1.5 L water, and ingest 20 mg soil.

1999). Exposed populations are estimated to be 512,631 employees, of whom 198,249 are female. Exposures in occupational settings can occur through skin contact and by inhalation of vapors and dust. Phthalates are manufactured within closed systems, but workers can be exposed during filtering or loading/unloading of tank cars (NTP 2000). Higher exposures to phthalates can occur during incorporation of the phthalate in the final product (e.g., plastics) if the process runs at a high temperature. In a limited number of surveys, di-*n*-butyl phthalate levels in production facilities in the United States have ranged from concentrations below the detection limit (0.01–0.02 mg/m^3) to 0.08 mg/m^3 (NTP 2000). Following a review of six studies, the American Chemistry Council has estimated exposure to di-*n*-butyl phthalate in the workplace based upon an assumed level of 1 mg/m^3 in the air during the production of phthalates (NTP 2000). Exposure levels during incorporation of di-*n*-butyl phthalate into plastic are not known. An exposure level was estimated by using assumptions of a 10 m^3/day inhalation and a 70 kg body weight. The resulting exposure estimate was 143 µg/kg body weight/workday for workers employed in phthalate manufacturing (NTP 2000).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Studies from Europe and Canada suggest that children may be exposed to di-*n*-butyl phthalate from food. However, little information is available that would allow an estimation of exposures from food and the differences between adult and child diets from U.S. studies. Infant food from Germany had only traces of di-*n*-butyl phthalate at levels ranging from not detected (i.e., <0.01 mg/kg) to 0.03 mg/kg (Bruns-Weller and Pfordt 2000a, 2000b). Mother's milk samples from German women also contained low amounts of

di-*n*-butyl phthalate at concentrations in the range of 0.01–0.05 mg/kg. Di-*n*-butyl phthalate was detected in infant formula from Great Britain at concentrations ranging from 0.08 to 0.40 mg/kg (dry weight basis) in 1996 and <0.05–0.09 mg/kg (dry weight basis) in 1998 (MAFF 1996b, 1998). While di-*n*-butyl phthalate has been found in food in the United States, mainly fish, it is difficult to determine how widespread contamination of food is, based on the available information, some of which is >20 years old.

Chan and Meek (1994) estimated the daily intake of di-*n*-butyl phthalate by children in Canada (see Table 6-4). Based on the medium-specific intakes, it is estimated that the average daily intake of di-*n*-butyl phthalate for age groups from 0–11 years in the general population in Canada range from 2.4 to 5.0 µg/kg body weight/day. In Great Britain, the range of average exposure from infant formula was 2.4 and 1.4 µg/kg body weight/day at birth and 6 months, respectively, in 1998 (MAFF 1998). In 1996, the average exposures from infant formula were 14 and 9.3 µg/kg body weight/day at birth and 6 months, respectively.

Children, and especially small children, may be exposed to elevated levels of di-*n*-butyl phthalate from chewing on soft plastic material if it contains this chemical as a plasticizer; however, it is unclear exactly what products may contain di-*n*-butyl phthalate. Di-*n*-butyl phthalate can migrate from plastics into surrounding media, including saliva and air. For example, Lygre et al. (1993) reported that di-*n*-butyl phthalate in denture material (polymethyl methacrylate) leached into saliva in the mouths of adult patients with new dentures. The concentration range was not detected–7.5 mg/L with a mean concentration of 0.1 mg/L. Out of 11 adult patients, 7 had detectable levels of di-*n*-butyl phthalate. No di-*n*-butyl phthalate was detected in the saliva of adult patients with old dentures or in the controls (the detection limit was 0.1 mg/L). In addition, 0.04 mg/m^3 of di-*n*-butyl phthalate, which had volatilized from paint, was detected in indoor air (Crump 1995). Cadogan and Howick (1996) reported that an indoor overall emission rate of 2.3x10^{-4} mg/second-m^3 at 25 EC has been calculated for all phthalate plasticizers in products such as wall coverings, flooring, upholstery, and wire insulation. Since the physical processes associated with the leaching of plasticizers from plastics should be the same for all plastics, it is anticipated that di-*n*-butyl phthalate will also migrate from other plastics to whatever medium is present at the plastic interface. Di-*n*-butyl phthalate is used in vinyl flooring and floor wax, and children, especially young children, often crawl and play on floors. No data are available that allow a quantification of the number or types of plastic products that contain di-*n*-butyl phthalate as a plasticizer; however, latest public production figures show that approximately 6,662 metric tons (1.5x10^7 pounds) of di-*n*-butyl

phthalate were produced in the United States in 1993 (see Chapter 5). Some plastics can contain >50% plasticizer (Cadogan and Howick 1996) and, based on the presence of di-*n*-butyl phthalate in the air and water, at least some of this is likely to escape either by volatilization or other transfer process to the surrounding material (e.g., saliva, skin, water). Thus, it appears that children may be more highly exposed to di-*n*-butyl phthalate than adults because they are potentially exposed dermally while lying on floors and carpets, and by inhalation by playing near potential sources such as flooring and carpeting. Mouthing of toys is another potential source of oral phthalate exposure in children. However, use of di-*n*-butyl phthalate in toys appears to be rare. In an analysis of 17 plastic toys, di-*n*-butyl phthalate was detected in one polyvinyl chloride doll's head at 0.01% by weight (Rastogi 1998). No information, however, is available that would allow the confirmation of this possibility or the quantification of the potential exposures.

There are no specific examples of di-*n*-butyl phthalate contamination in homes resulting from inadvertent transport to the home from workplace exposures.

Young children sometimes ingest soil either intentionally through pica (the desire to eat substances, such as soil or chalk, not normally eaten) or unintentionally through hand-to-mouth activity. While no childhood exposures to di-*n*-butyl phthalate from soil ingestion or dermal soil exposure have been documented, this phthalate has been detected in soil. In addition, di-*n*-butyl phthalate has also been detected in atmospheric fallout in both urban and rural areas, and is not expected to migrate rapidly to groundwater or to volatilize rapidly from soil surfaces. Nonetheless, di-*n*-butyl phthalate is anticipated to degrade rapidly, and exposures to this chemical from other sources are anticipated to be much greater. Therefore, exposures of children to di-*n*-butyl phthalate from soil would likely be slight. No information is available on the absorption in the stomach (bioavailability) of di-*n*-butyl phthalate in soil to children.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Individuals who manufacture or use plasticizers probably 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. Certain cosmetics, such as nail polish, contain di-*n*-butyl phthalate, and higher exposures may result to consumers of these products. In addition, since many plastic articles contain di-*n*-butyl phthalate and many of these are used in homes and businesses, indoor concentrations may be higher than outdoor concentrations, as has been reported (see

Section 6.4.1 above). Therefore, populations that work indoors may be exposed to higher concentrations than those who work outdoors. Insufficient information is available to quantify any differences.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of di-*n*-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 the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. Data are available on the physical and chemical properties of di-*n*-butyl phthalate (see Chapter 4), and further research in this area does not appear to be required. Nonetheless, measurements of properties such as water solubility, vapor pressure, and octanol/water partition coefficient are technically difficult because di-*n*-butyl phthalate and other phthalates are ubiquitous contaminants in the environment and are contaminates of laboratory air and surfaces, making accurate measurements difficult. Hence, a set of data that are very carefully determined are needed.

Production, Import/Export, 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, no publicly available current production data are available. In addition, in the specialty plasticizer market, the amount of specific plasticizers used in various applications are not available and data may change over time. Authoritative sources of current data on production, 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.

Environmental Fate. Biodegradation is well described in the literature, and the importance of hydrolysis reactions can be inferred from sterile controls reported with biodegradation studies. Major gaps are present in the understanding of partitioning and transport of di-*n*-butyl phthalate in water. For example, the log K_{oc} of di-*n*-butyl phthalate is reported to be 3.14 (see Chapter 4), which indicates that the majority of di-*n*-butyl phthalate in water will be sorbed to sediments or suspended particles. Many reports, however, have measured the dissolved/sorbed concentration of di-*n*-butyl phthalate in environmental samples and have found that, in some cases, in excess of 70% of the di-*n*-butyl phthalate is in the dissolved state. A greater knowledge of this process would allow a more comprehensive understanding of the exposure potential for aquatic organisms to di-*n*-butyl phthalate. Similarly, a better understanding of the partitioning of di-*n*-butyl phthalate on atmospheric particles and their washout/ fallout characteristics would also allow better exposure assessments.

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 of di-*n*-butyl phthalate that is bound to soils, sediments, and air particulates by the inhalation, oral, and dermal routes, are needed to assess 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. Numerous studies have shown that the accumulation of di-*n*-butyl phthalate in the aquatic and terrestrial food chain is limited by biotransformation, which progressively increases with trophic level (Staples et al. 1997). Therefore, di-*n*-butyl phthalate will not biomagnify through the food chain.

Exposure Levels in Environmental Media. Information on exposure levels in the environment is 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. No data are available showing the concentration of di-*n*-butyl phthalate in common plastic consumer products. A list of the composition of common plastic consumer products and the amount of di-*n*-butyl phthalate that they contain would allow a much better estimation of exposures from these products. Di-*n*-butyl phthalate has been extensively monitored in food in Europe and Canada, but very little information is available about the U.S. food supply. This type of information, especially information about infant foods and mother's milk, would permit an estimation of the importance of food in di-*n*-butyl phthalate exposures. In addition, di-*n*-butyl phthalate is an indirect food additive present in food containers, and the extent to which it migrates into food would allow a better estimation of exposures from food. While some information about migration is available from European studies, information on migration from packaging meeting U.S. standards would allow better assessments of exposures from food. In addition, 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. Moreover, information relating exposure levels to levels in humans are needed to assess risks to populations surrounding hazardous waste sites.

Exposures of Children. A number of studies are available that report di-*n*-butyl phthalate concentrations in infant foods and mother's milk in Europe. Similar studies are not available for U.S. sources, and this information could be used to better estimate the importance of food as a source of di-*n*-butyl phthalate exposures to children. No data are available that allow the estimation of exposures resulting from mouthing and/or chewing on plastics or other compounds containing di-*n*-butyl phthalate. It is possible that the majority of plastic toys used by children contain plasticizers, and the extent to which these contain di-*n*-butyl phthalate is not known. A complete study of the migration of di-*n*-butyl phthalate from plastics and other compounds into saliva, including the effects of chewing, also has not been performed. This information would allow a much better estimation of children's exposure to di-*n*-butyl phthalate. It is known that di-*n*-butyl phthalate migrates from polymethyl methacrylate denture material into saliva (see Lygre et al. 1993); however, dentures are present in the mouth for long periods, and the applicability of this study to di-*n*-butyl phthalate migration from plastic and other materials to saliva in children's mouths is unclear. In addition to the potential migration of di-*n*-butyl phthalate from plastic and other materials to saliva, the potential also exists for dermal and inhalation exposures. Di-*n*-butyl phthalate is also used in cosmetics, such as nail polish, and children may play with some of these products. The extent to which these products contain di-*n*-butyl phthalate is not known. While it is much more likely that exposures will occur from plastics and other materials, no data are available on childhood exposures to di-*n*-butyl phthalate from soil either from ingestion or from dermal exposure.

Child health data needs relating to susceptibility are discussed in Section 3.12.2 Identification of Data Needs: Children's Susceptibility.

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.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2000) database provides information on ongoing studies; however, none were found that fill any of the data needs identified in Section 6.8.1.

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

7. ANALYTICAL METHODS

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

Di-*n*-butyl phthalate may be determined by high resolution gas chromatography with an electron capture detector (HRGC/ECD) (EPA 1984b), gas chromatography/mass spectrometry (GC/MS) (EPA 1994a), gas chromatography with a flame ionization detector (GC/FID) (NIOSH 1994), gas chromatography/Fourier transform infrared spectrometry (GC/FTIR) (EPA 1994b), high performance liquid chromatography/mass spectrometry (HPLC/MS) (Coldham et al. 1998), or high performance liquid chromatography/ion-trap mass spectrometry (HPLC/Ion Trap-MS) (Coldham et al. 1998). 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 in Sections 7.1 and 7.2.

Phthalates are common environmental contaminants that frequently contaminate laboratory glassware, sampling equipment, and solvents used to extract di-*n*-butyl phthalate from various media for analysis (Staples et al. 1997). As a result, it is difficult to make accurate measurements at low levels (<10 ppb). Care must be taken to preclude environmental and other samples from contamination with di-*n*-butyl phthalate.

7.1 BIOLOGICAL SAMPLES

Since di-*n*-butyl phthalate is relatively nonvolatile 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 cleanup steps may be required to separate fats and other endogenous lipophilic materials in the samples that co-extract from the biological material (Walters 1986). Several analytical methods for the determination of di-*n*-butyl phthalate in biological materials are listed in Table 7-1.

Recently, Blount et al. (2000) summarized a methodology to detect di-*n*-butyl phthalate metabolites in urine. In humans or animals, di-*n*-butyl phthalate is metabolized to mono-*n*-butyl phthalate and oxidative products, which are excreted through the urine and feces. Human urine samples are processed by β-glucuronidase hydrolysis (to release the mono phthalate ester) followed by solid-phase extraction. The eluate is concentrated; mono-*n*-butyl phthalate is chromatographically resolved by reverse-phase HPLC, detected by negative ion atmospheric pressure chemical ionization (APCI) tandem mass spectrometry, and quantified by isotope dilution.

7.2 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 in water may be separated without solvents by adsorption onto a suitable polymer such as Tenax (Pankow et al. 1988). Analytical methods for the determination of di-*n*-butyl phthalate in environmental samples are given in Table 7-2.

7.3 ADEQUACY OF THE DATABASE

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

Table 7-1. Analytical Methods for Determining Di-*n*-butyl Phthalate in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	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
Bile (cattle)	Extraction, fractionation by cation and anion exchange chromatography, β-glucuronidase/sulphatase hydrolysis	HPLC/Ion Trap-MS; HPLC/MS	No data	93.5±4.4%	Coldham et al. 1998
Blood plasma (cattle)	Extraction, fractionation by cation and anion exchange chromatography, β-glucuronidase/sulphatase hydrolysis	HPLC/Ion Trap-MS; HPLC/MS	No data	89.6±1.6%	Coldham et al. 1998
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	Removal with nitrogen gas trap, extraction with diethyl ether	GC/MS	No data	No data	Ho et al. 1983
Urine (cattle)	Extraction, fractionation by cation and anion exchange chromatography, β-glucuronidase/sulphatase hydrolysis	HPLC/Ion Trap-MS; HPLC/MS	No data	76.2±2.3%	Coldham et al. 1998
Urine	β-glucuronidase hydrolysis, solid-phase extraction	HPLC/APCI-MS	0.6 ng/mL	>90%	Blount et al. 2000

APCI = negative ion atmospheric pressure chemical ionization; ECD = electron capture detector; GC = gas chromatography; HPLC = high performance liquid chromatography; HRGC = high resolution gas chromatography; MS = mass spectrometry

Table 7-2. Analytical Methods for Determining Di-*n*-butyl Phthalate in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Recovery	Reference
Air	Adsorption/solvent extraction with cellulose ester membrane	NIOSH 5020 GC/FID	1–20 mg/m^3 20 L air sample	No data	NIOSH 1994
Water	Extract with dichloromethane, exchange to hexane, concentrate	EPA 625 HRGC/ECD	2.5 µg/L	80±6%[a]	EPA 1984b
Water	Extract with dichloromethane, exchange to hexane, concentrate	EPA 606 HRGC/ECD	0.36 µg/L	80±6%[a]	EPA 1984b
Liquid	EPA Extraction Method 3510 using dichloromethane followed by cleanup	EPA 8061 GC/ECD	0.33 µg/L	76.5–108%	EPA 1996b
Groundwater	EPA Extraction Methods 3510 or 3520 using dichloromethane followed by cleanup	EPA 8250A GC/MS	2.5 µg/L[a]	76%	EPA 1994a
Wastes, non-water miscible	Extract with dichloromethane followed by cleanup	EPA 8410 GC/FT-IR	10 µg/L	No data	EPA 1994b
Wastes, non-water miscible	Extract with dichloromethane, cleanup, exchange to hexane	EPA 8060 GC/ECD or FID	36 mg/kg	96%	EPA 1986a
Wastes, non-water miscible	EPA Extraction Methods 3510 or 3520 using dichloromethane followed by cleanup	EPA 8270 GC/FT-IR	50 mg/kg	76%	EPA 1998l
Soil	Extraction using dichloromethane/acetone(1:1), followed by cleanup	EPA 8061 GC/ECD	0.33 µg/L	90–95%	EPA 1996b
Soil	Extract with dichloromethane, cleanup, exchange to hexane followed by cleanup	EPA 8060 GC/ECD or FID	2.4×10^{-4} mg/kg	96%	EPA 1986a

Table 7-2. Analytical Methods for Determining Di-*n*-butyl Phthalate in Environmental Samples *(continued)*

Sample matrix	Preparation method	Analytical method	Sample detection limit	Recovery	Reference
Soil	EPA Extraction Methods 3510 or 3520 using dichloromethane followed by cleanup	EPA 8250A GC/MS	1.7 mg/kg	96%	EPA 1994a
Soil/sediment	Extract with dichloromethane followed by cleanup	EPA 8410 GC/FT-IR	10 µg/L[b]	No data	EPA 1994b
Soil/sediment	EPA Extraction Methods 3510 or 3520 using dichloromethane followed by cleanup	EPA 8270 GC/FT-IR	0.66 mg/kg	76%	EPA 1998l

[a]Relative recovery, percent, ±standard deviation
[b]Detection limits for some samples may be several orders of magnitude higher depending upon the sample characteristics and extraction procedure employed.

ECD = electron capture detector; FID = flame ionization detector; FT-IR = Fourier transform-infrared spectrometer; GC = gas chromatography; MS = mass spectrometry

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

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Sensitive and selective methods using high resolution GC or HPLC are available for the qualitative and quantitative measurement of 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 (EPA 1986g). 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 (see Staples et al. 1997). Since health effects appear to 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. HPLC/MS has been adapted to measure body levels of metabolites of di-*n*-butyl phthalate, primarily mono-*n*-butyl phthalate, which have the potential to be biomarkers of exposure (Blount et al. 2000).

No information was located concerning biomarkers of effect of di-*n*-butyl phthalate. Precise, accurate, reliable, and specific methods for measuring background levels of biomarkers of effect in the population, as well as the levels at which health effects may occur, are needed.

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 methods of extraction followed by high resolution GC (with derivatization of sample) or HPLC-MS have

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 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.

7.3.2 Ongoing Studies

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).

A search of Federal Research in Progress reported no ongoing studies relating to analytical methods development (FEDRIP 2000).

8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding di-*n*-butyl phthalate in air, water, and other media are summarized in Table 8-1.

An MRL of 0.5 mg/kg/day has been derived for acute-duration oral exposure to di-*n*-butyl phthalate based on a NOAEL of 50 mg/kg/day for developmental effects in the offspring of rats orally exposed by gavage to di-*n*-butyl phthalate on gestational days 12–21 (Mylchreest et al. 2000).

A chronic MRL for DNB was not derived. There were no adequate chronic-duration oral studies identified for humans or animals. EPA verified an RfD of 0.1 mg/kg/day based on a study by Smith (1953)(IRIS 1999). In this study, 10 rats were fed diets containing 0.01-1.25 % dibutyl phthalate. Half of the high dose group died within the first week of exposure. ATSDR did not have confidence in this study to derive an MRL due to the lack of detail and apparent conflict in the reported results. EPA also had low confidence in the study; the RfD received a low rating.

The health effects data for di-*n*-butyl phthalate were evaluated by EPA and determined to be inadequate for derivation of an inhalation RfC; the RfC is considered not verifiable (IRIS 1999).

Table 8-1. Regulations and Guidelines Applicable to Di-*n*-butyl Phthalate

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenic classification	No data	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV-TWA	5 mg/m^3	ACGIH 2000
EPA	RAC	100 µg/m^3	EPA 2001p 40CFR266 Appendix IV
NIOSH	REL (TWA) IDLH	5 mg/m^3 4,000 mg/m^3	NIOSH 2001
OSHA	PEL (8-hour TWA) General industry	5 mg/m^3	OSHA 2001c 29CFR1910.1000 Table Z-1
	PEL (8-hour TWA) Construction industry	5 mg/m^3	OSHA 2001b 29CFR1926.55 Appendix A
	PEL (8-hour TWA) Shipyard industry	5 mg/m^3	OSHA 2001a 29CFR1915.1000
USC	HAP		USC 2001 42USC7412
b. Water			
DOT	Marine pollutant		DOT 2001b 49CFR172.101 Appendix B
EPA	Effluent guidelines—aluminum forming point source category TTO	 >0.01 mg/L	EPA 2001h 40CFR467.02
	Effluent guidelines—coil coating point source category TTO	 >0.01 mg/L	EPA 2001g 40CFR465.02
	Effluent guidelines—metal finishing point source category TTO	 >0.01 mg/L	EPA 2001q 40CFR433.11

Table 8-1. Regulations and Guidelines Applicable to Di-*n*-butyl Phthalate *(continued)*

Agency	Description	Information	References
NATIONAL *(cont.)*			
EPA	Effluent guidelines; steam electric power generating point source category—priority pollutants		EPA 2001o 40CFR423 Appendix A
	Human health consumption		EPA 1999c
	Water and organism	2.7 mg/L	
	Organism only	12 mg/L	
	NPDES—permit application testing requirements	Organic toxic pollutants in each of four fractions in analysis by GC/MS volatiles	EPA 2001l 40CFR122 Appendix D Table II
	NPDES—permit testing requirements for publicly owned treatment works		EPA 2001m 40CFR122 Appendix J Table 2
	Process waste water discharges resulting from the manufacture of bulk organic chemicals		EPA 2001a 40CFR414.70
	Standards for owners/operators of hazardous waste TSD facilities— groundwater monitoring (PQL)	5 µg/L	EPA 2001i 40CFR264 Appendix IX
	Toxic pollutant effluent limitations and standards for direct discharge point sources that use end-of-pipe biological treatments—effluent limitations		EPA 2001u 40CFR414.91(b)
	Maximum for any 1-day	57 µg/L	
	Maximum for any monthly average	27 µg/L	
	Toxic pollutant effluent limitations and standards for direct discharge point sources that do not use end-of-pipe biological treatments—effluent limitations		EPA 2001v 40CFR414.101(b)
	Maximum for any 1-day	43 µg/L	
	Maximum for any monthly average	20 µg/L	

Table 8-1. Regulations and Guidelines Applicable to Di-*n*-butyl Phthalate *(continued)*

Agency	Description	Information	References
NATIONAL *(cont.)*			
EPA	Toxic pollutant standards for indirect discharge point sources—effluent limitations		EPA 2001w 40CFR414.111(b)
	Maximum for any 1-day	43 µg/L	
	Maximum for any monthly average	20 µg/L	
	Water quality standards—toxics criteria for those states not complying with Clean Water Act Section 303(c)(2)(B)	No data	EPA 2001t 40CFR131.36
c. Food			
FDA	Indirect food additive—adhesives and components of coating		FDA 2000a 21CFR175.105
	Indirect food additive—adhesives and components of coatings; catalysts and cross-linking agents for epoxy resins	For use only in coatings for containers having a capacity of 1,000 gallons or more when intended for repeated use in contact with alcoholic beverages containing up to 8% of alcohol by volume	FDA 2000f 21CFR175.300(b)
	Indirect food additive—limitations on cellophane for food packaging	Alone or in combination with other phthalates—total phthalates do not exceed 5%	FDA 2000b 21 CFR 177.1200
	Indirect food additive—paper and paperboard components		FDA 2000d 21CFR176.170
	Indirect food additive—paper and paperboard components	Adjuvant substances permitted to be used in the preparation of slimicides	FDA 2000g 21CFR176.300(d)

Table 8-1. Regulations and Guidelines Applicable to Di-*n*-butyl Phthalate *(continued)*

Agency	Description	Information	References
NATIONAL *(cont.)*			
FDA	Indirect food additive—polyester resins, cross-linked; solvents for inhibitors, accelerators, and catalysts	Quantity used does not exceed that reasonably required to accomplish intended physical or technical effect	FDA 2000e 21CFR177.2420(b)
	Indirect food additives—rubber articles intended for repeated use	Total not to exceed 30% by weight of rubber product	FDA 2000c 21CFR177.2600
d. Other			
ACGIH	BEI Carcinogenic classification	No data	ACGIH 2000
CPSC	Consumer product limits	No data	
DOT	Reportable quantity	10 pounds	DOT 2001a 49CFR172.101 Appendix A Table 1
EPA	Carcinogenic classification	Group D[a]	IRIS 2001
	RfD	0.1 mg/kg/day	
	Designated hazardous substance		EPA 2001c 40CFR116.4
	Health and environmental protection standards for uranium and thorium mill tailings—listed constituent		EPA 2001k 40CFR192 Appendix I
	Identification and listing of hazardous waste	U069	EPA 2001f 40CFR261.33
	Land disposal restrictions—universal treatment standards		EPA 2001x 40CFR268.48(a)
	Wastewater standard	0.057 mg/L[2]	
	Nonwastewater standard	28 mg/kg[3]	
	Municipal solid waste landfills—hazardous inorganic and organic constituents		EPA 2001j 40CFR258 Appendix II
	Suggested method	8060 8270	
	PQL	5 µg/L 10 µg/L	

Table 8-1. Regulations and Guidelines Applicable to Di-*n*-butyl Phthalate *(continued)*

Agency	Description	Information	References
NATIONAL *(cont.)*			
EPA	Pollutants eligible for a removal credit	If requirements for total hydrocarbons are met when sewage sludge is fired in a sewage sludge incinerator	EPA 2001n 40CFR403 Appendix G
	Reportable quantity	100 pounds	EPA 2001d 40CFR302.4
	Toxic chemical release reporting; Community Right-to-Know—effective date	01/01/87	EPA 2001b 40CFR372.65
	TSCA—health and safety data reporting; studies not subject to the reporting requirements		EPA 2001r 40CFR716.120(c)
	TSCA—testing consent order for environmental effects	01/09/89	EPA 2001s 40CFR799.5000
STATE			
Regulations and Guidelines:			
a. Air			
Arkansas	RAC	100 µg/m^3	BNA 2001
California	RAC	100 µg/m^3	BNA 2001
Delaware	RAC	100 µg/m^3	BNA 2001
Idaho	Toxic air pollutants OEL EL AAC	 5.0 mg/m^3 0.333 pounds/hour 0.25 mg/m^3	BNA 2001
Illinois	RAC	100 µg/m^3	BNA 2001
Kansas	Ambient air quality standards	10 tons/year	CDC 1999
Kentucky	RAC	100 µg/m^3	BNA 2001
Minnesota	HAP threshold	10 tons/year	BNA 2001
New Hampshire	Regulated toxic air pollutant OEL	 5 mg/m^3	BNA 2001
Rhode Island	HAP		BNA 2001
STATE *(cont.)*			

Table 8-1. Regulations and Guidelines Applicable to Di-*n*-butyl Phthalate *(continued)*

Agency	Description	Information	References
South Carolina	RAC	100 µg/m^3	BNA 2001
	Toxic air emissions—maximum allowable concentration	25 µg/m^3	BNA 2001
Tennessee	RAC	100 µg/m^3	BNA 2001
Vermont	Hazardous ambient air standard Averaging time Action level (8-hours)	500 µg/m^3 8 hours 21 pounds	BNA 2001
Wisconsin	<25 ft $25 ft <75 ft $75 ft	0.269 pounds/hour 1.04 pounds/hour 8.11 pounds/hour	Wisconsin DNR 2001
	Ambient air concentrations	120 µg/m^3	
Wyoming	RAC	100 µg/m^3	BNA 2001
b. Water			
Alaska	Groundwater clean-up level	3.65 mg/L	BNA 2001
Arkansas	Goundwater monitoring (PQL)	5 µg/L	BNA 2001
Delaware	Freshwater Fish ingestion only Fish and water ingestion Marine/Estuarine Fish and shellfish ingestion	 13 mg/L 2.8 mg/L 2.1 mg/L	BNA 2001
Florida	Drinking water guideline	0.7 mg/L	HSDB 2001
Georgia	Instream concentration	12.1 mg/L	BNA 2001
Illinois	Groundwater monitoring (PQL)	5 µg/L	BNA 2001
Kentucky	Hazardous constituents for groundwater monitoring (PQL)	5 µg/L	BNA 2001
	Maximum allowable instream concentration	2.7 mg/L	BNA 2001
Louisiana	Groundwater monitoring (PQL)	5 µg/L	BNA 2001
Maine	Drinking water guideline	0.22 mg/L	HSDB 2001
Massachusetts	Groundwater monitoring (PQL)	5 µg/L	BNA 2001
Michigan	Groundwater quality treatment technology standard	35 µg/L	BNA 2001
Minnesota	Drinking water guideline	0.7 mg/L	HSDB 2001

STATE *(cont.)*

Table 8-1. Regulations and Guidelines Applicable to Di-*n*-butyl Phthalate *(continued)*

Agency	Description	Information	References
Nebraska	Aquatic life criteria		BNA 2001
	Acute	No data	
	Chronic	12 mg/L	
New Hampshire	Drinking water guideline	0.8 mg/L	HSDB 2001
	Water quality criteria		BNA 2001
	Water and fish ingestion	2.7 mg/L	
	Fish consumption only	12 mg/L	
	Ambient groundwater quality standard	34 mg/L	BNA 2001
New Jersey	Groundwater quality criteria	900 µg/L	BNA 2001
	PQL	20 µg/L	
New Mexico	Groundwater parameter (PQL)	0.01 mg/L	BNA 2001
New York	Groundwater monitoring (PQL)	5 µg/L	BNA 2001
Oklahoma	Hazardous constituent (PQL)	5 µg/L	BNA 2001
South Carolina	Water quality criteria		BNA 2001
	Organism consumption	12 mg/L	
	Groundwater monitoring (PQL)	5 µg/L	
Vermont	Consumption of water and organism	2.7 mg/L	BNA 2001
	Consumption of organism only	12 mg/L	
Virginia	Hazardous constituent (PQL)	5 µg/L	BNA 2001
	Public water supply	2.7 mg/L	BNA 2001
	All other surface waters	12 mg/L	
Wisconsin	Drinking water guideline	0.1 mg/L	HSDB 2001
	Groundwater standard		BNA 2001
	Enforcement standard	100 mg/L	
	Preventive action limit	20 mg/L	
c. Food		No data	
d. Other			
Alabama	RfD	0.1 mg/kg/day	BNA 2001
Delaware	Direct exposure criteria for soil		BNA 2001
	Residential	1,000 ppm	
	Industrial/commercial	2,500 ppm	
Massachusetts	RfD	0.1 mg/kg/day	BNA 2001
STATE *(cont.)*			
Minnesota	RfD	0.1 mg/kg/day	BNA 2001
	Health risk limit	700 µg/L	

Table 8-1. Regulations and Guidelines Applicable to Di-*n*-butyl Phthalate *(continued)*

Agency	Description	Information	References
Missouri	Hazardous constituents		BNA 2001
New York	Reportable quantity		BNA 2001
	Air	10 pounds	
	Land/water	1 pound	

[a]Group D: inadequate or no human and animal evidence of carcinogenicity

AAC = acceptable ambient concentrations; ACGIH = American Conference of Governmental Industrial Hygienists; BEI = biological exposure index; BNA = Bureau of National Affairs; CDC = Center for Disease Control; CFR = Code of Federal Regulations; CPSC = Consumer Product Safety Commission; DNR = Department of Natural Resources; DOT = Department of Transportation; EL = emissions level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; GC/MS = gas chromatography/mass spectroscopy; HAP = hazardous air pollutant; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; IRIS = Integrated Risk Information System; NIOSH = National Institute of Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; OEL = occupational exposure level; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation limit; RAC = reference air concentration; REL = recommended exposure limit; RfD = oral reference dose; TLV = threshold limit value; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TTO = total toxic organics; TWA = time-weighted average; USC = United States Code

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

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

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

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

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

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

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

Biomarkers—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.

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

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

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

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

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.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

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 occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (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.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

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

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

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.

Immunological Effects—Functional changes in the immune response.

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 has been reported 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 exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

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

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

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

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 no-observed-adverse-effect level (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 the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

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

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) 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 Threshold Limit Value - Time Weighted Average (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)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

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

Toxic Dose$_{(50)}$ (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.

Toxicokinetic—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A
ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Di-*n*-butyl phthalate
CAS Number: 84-74-2
Date: June 30, 2001
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to Figure: 21
Species: Rats

Minimal Risk Level: 0.5 [X] mg/kg/day [ ] mg/m^3

Reference: Mylchreest E, Wallace DG, Cattley RC, et al. 2000. Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to di(n-butyl) phthalate during late gestation. Toxicol Sci 55:143-151.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of 20 pregnant Sprague-Dawley rats (except 11 in the 500 mg/kg/day group) were treated with 0, 0.5, 5, 50, 100, or 500 mg/kg/day di-*n*-butyl phthalate by gavage in corn oil on gestation days 12–21. Dams were examined daily for clinical signs of toxicity, body weight was recorded daily during treatment, and food intake was recorded twice weekly. Dams were killed on postpartum day 21, examined grossly, and the weights of liver, kidneys, adrenals, uterus, and ovaries, and numbers of implantation sites were recorded. On postpartum day 1, numbers of live and dead pups, clinical signs of toxicity, pup weight, and ano-genital distance were recorded. Additionally, the location and number of nipples and areolas were recorded for male pups on postpartum day 14. From postpartum day 30 (females) or 38 (males), pups were examined daily for vaginal opening or preputial separation, respectively, until occurrence. Pups were killed at sexual maturity (postpartum day 110±10 days for males; 80±5 days for females), weighed, and internal and external genitalia were examined for malformations and undescended testes. Organs were weighed, and right testis and epididymides were examined histologically.

Effects noted in study and corresponding concentrations: No developmental effects or clinical signs of toxicity were seen in pups exposed to 50 mg/kg/day or less *in utero*. The only treatment-related effect seen in the 100 mg/kg/day group was retained areolas and nipples in males (normally seen only in females) on postpartum day 14. This effect was dose-dependent, being more prominent at 500 mg/kg/day. Permanence of retained areolas and nipples was not assessed. Other statistically significant effects, seen only in males at 500 mg/kg/day level, were decreased AGD (12% decrease) and ano-genital distance/body weight at birth; smaller epididymides, dorsolateral prostate, and levator ani-bulbocavernosus muscle at sexual maturity; and decreased testes weight (when animals with enlarged testes were excluded). Malformations of the male reproductive tract included absent or malformed epididymis, absent or malformed vas deferens, hypospadia, and unilaterally absent seminal vesicle. Histopathological lesions of the testis seen were seminiferous tubule degeneration, focal interstitial hyperplasia, and adenoma. In males, no significant changes were seen in age at preputial separation, or body, kidney, liver, adrenal, ventral prostate, vas deferens, seminal vesicle, or other organ weights (other than those listed above). In female pups, no significant differences from controls were seen in age of onset of vaginal opening; body, liver, kidney, adrenal, ovary, or uterus weight; or gross morphology of the reproductive organs at sexual maturity.

Concentration and end point used for MRL derivation: Increased incidence of retained areolas and nipple in the male offspring of rats exposed to $100 mg//kg/day; no effects were observed at 50 mg/kg/day.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? NA

Other additional studies or pertinent information that lend support to this MRL: A number of developmental effects involving androgenic-dependent tissues have been observed in acutely or longer exposed rats; these include decreases in anogenital distance and anogenital distance/body weight ratio, increased number of retained nipples, and decreased androgen-dependent tissue weights (ventral prostate, epididymis, cauda epididymis, testes, glans penis, and levator ani-bulbocavernosus) (Ema et al. 1998, 2000b; Gray et al. 1999; Mylchreest et al. 1999, 2000).

Agency Contact (Chemical Manager): Jessilynn Taylor

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

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

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

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

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 3-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 9 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 3-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

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

SAMPLE

1 6

Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

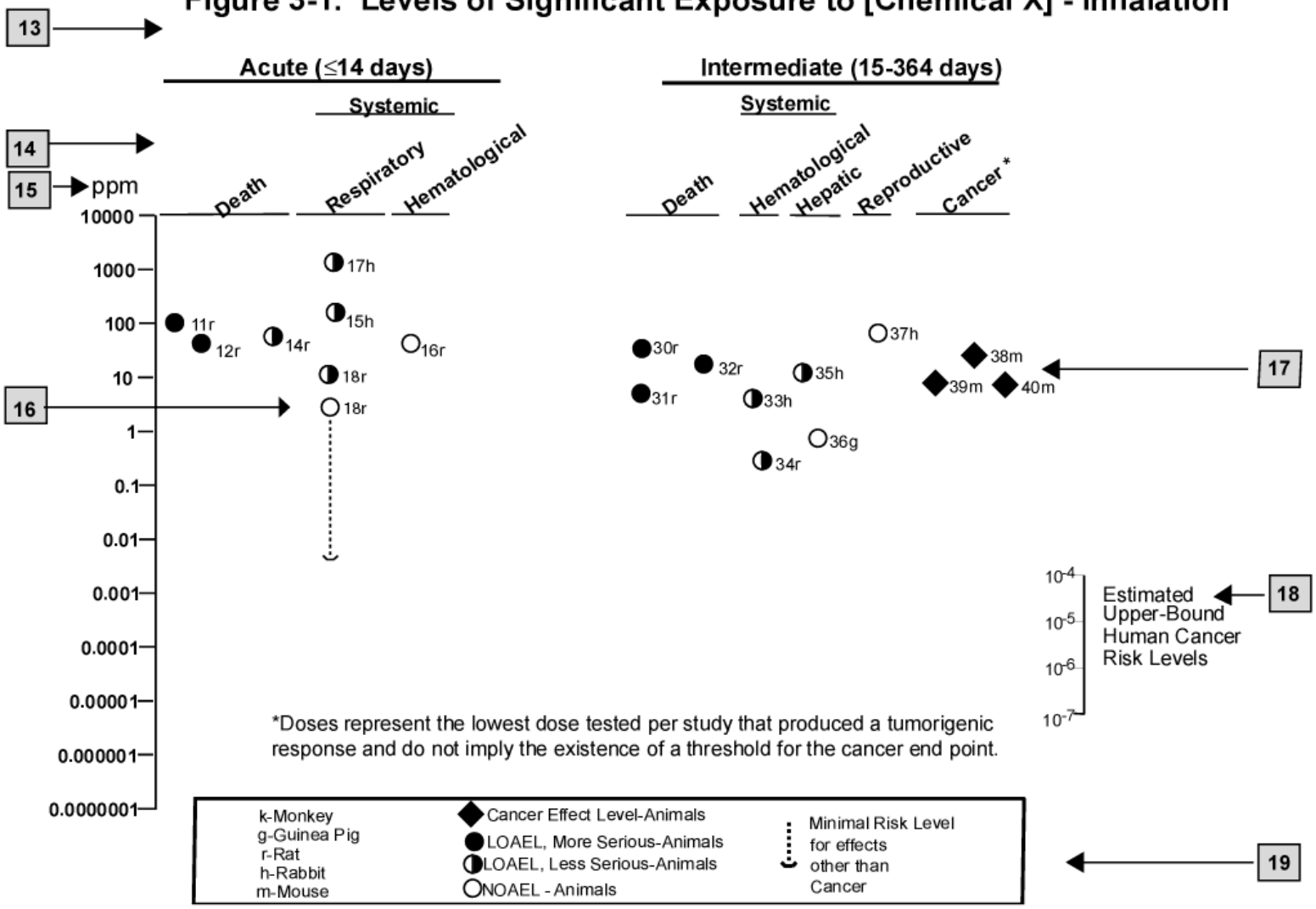
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 6 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 6 Systemic	9	9	9	9	9		9
4 6 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					9		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 3-1.

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram

EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter

mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector

pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

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

µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

APPENDIX D

INDEX