CHAPTER 6. 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 DEHP is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of DEHP.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk 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.

6.1 Information on Health Effects

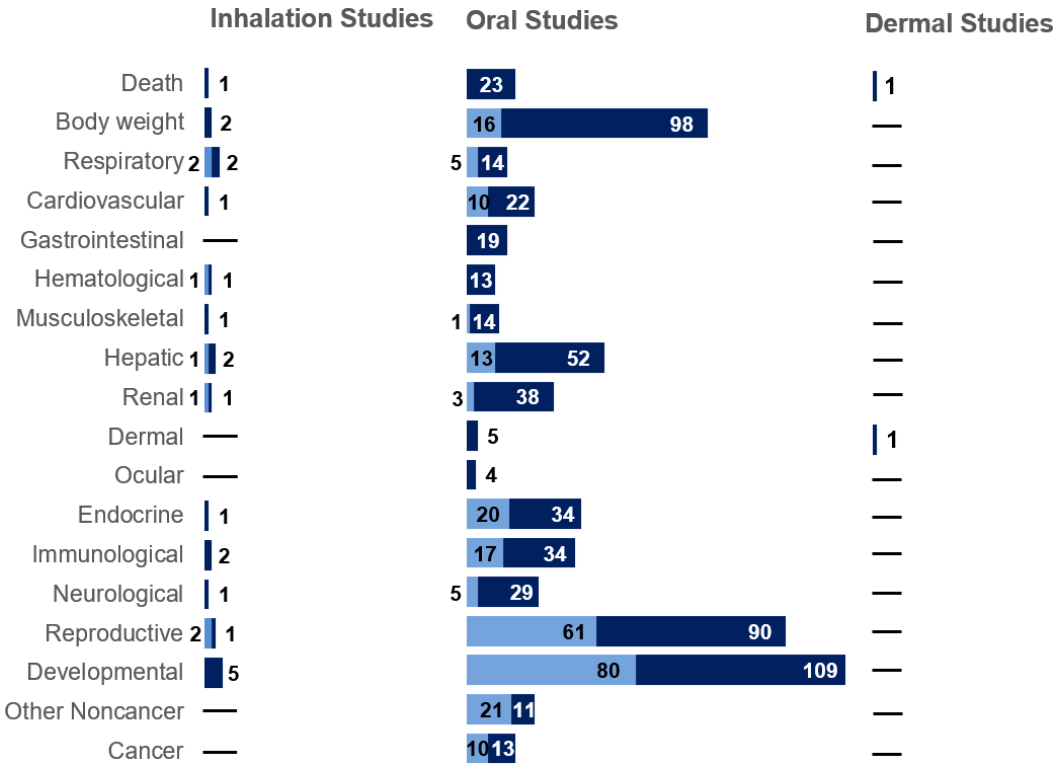
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to DEHP that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of DEHP. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

As noted in Section 2.1, both human and animal data were prioritized due to the extensive number of human and animal studies. Therefore, Figure 6-1 is not inclusive of the entire body of literature. The criteria for study prioritization are further discussed in Appendix B. The purpose of this figure is to illustrate the information concerning the health effects of DEHP.

As illustrated in Figure 6-1, most of the data on the toxicity of DEHP come from oral studies in laboratory animals. The most commonly examined endpoints were body weight, reproductive, and developmental effects. The laboratory animal toxicity database also consists of a small number of inhalation studies examining 30 endpoints and two acute dermal exposure studies.

Figure 6-1. Summary of Existing Health Effects Studies on DEHP By Route and Endpoint*

Oral exposure studies in animals comprised the majority of DEHP health effects research
The most studied endpoints (in **humans** & **animals**) were **potential body weight, reproductive, and developmental effects** resulting from oral exposure to animals



6.2 Identification of Data Needs

Missing information in Figure 6-1 should not 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.

Acute-Duration MRLs. The available acute inhalation database was not considered adequate for derivation of an MRL. Only two acute studies were identified, and the endpoints examined were limited to respiratory function and general developmental toxicity. Additional acute inhalation toxicity studies are needed; these studies should include examination of suspected sensitive targets including immune function, reproductive toxicity, and effects on development of the endocrine, reproductive, renal, and nervous systems. While the acute oral database was considered adequate for derivation of an MRL, a NOAEL value has not been established for the sensitive effect that serves as the basis of the MRL (altered glucose homeostasis in offspring). Additionally, NOAEL values have not been established for other sensitive effects following acute oral exposure (altered reproductive development in offspring, adult male reproductive effects). Similarly, potential adjuvant effects of DEHP, identified as a sensitive effect in longer-duration studies, have not been evaluated following acute oral exposure. Additional low-dose studies evaluating these endpoints could reduce uncertainty in the acute-duration oral MRL.

Intermediate-Duration MRLs. The available intermediate inhalation and oral databases were considered adequate for derivation of MRLs. However, a NOAEL value has not been established for either route for the most sensitive effect (toxicity to the developing reproductive system). Additional low-dose studies evaluating this endpoint could reduce uncertainty in the intermediate-duration MRLs.

Chronic-Duration MRLs. The absence of chronic-duration inhalation studies evaluating noncancer effects precluded derivation of a chronic MRL. Chronic toxicity studies examining a wide range of endpoints are needed to identify or confirm the most sensitive target and establish concentration-response relationships. The chronic oral database was also considered inadequate for derivation of an MRL. The lowest LOAELs identified were orders of magnitude higher than LOAELs observed in intermediate studies (although they were for different health endpoints), and more critical effects (e.g., immune function) were not evaluated. Lower-dose studies evaluating immune function following chronic exposure are needed.

Health Effects. Identification of data needs for health effects in animal studies is limited to sensitive targets of DEHP toxicity discussed in Chapter 1 and considered during derivation of MRLs.

Immunological. Low-exposure studies designed to identify a NOAEL for adjuvant effects of DEHP following oral exposure would decrease the uncertainties in the MRLs. In particular, studies evaluating these endpoints following acute or chronic oral exposure would fill current data gaps. Mechanistic studies would help determine mechanisms of action and human relevance.

Reproductive. Low-exposure studies designed to identify a NOAEL for reproductive effects of DEHP following oral and inhalation exposure would decrease the uncertainties in the MRLs. Additional mechanistic studies would help determine mechanisms of action and human relevance.

Developmental. Studies designed to evaluate effects on the developing endocrine, reproductive, renal, and/or neurological systems following inhalation exposure to multiple concentration levels, particularly low concentrations, during gestation and/or lactation would fill a current data gap in the inhalation database. Additionally, studies designed to identify a NOAEL for endocrine, reproductive, and renal developmental effects following oral exposure would decrease uncertainty in the MRLs. Additional mechanistic studies would help determine mechanisms of action and human relevance.

Epidemiology and Human Dosimetry Studies. Studies relating urinary metabolite levels to human exposure estimates via multiple exposure routes would facilitate the estimation of intakes associated with adverse effects and enable dose-response comparisons between humans and animals.

Biomarkers of Exposure and Effect. Additional data establishing an appropriate sampling interval for DEHP in urine and quantifying the rate of hydrolysis of DEHP to metabolites during storage of urine samples would help determine DEHP concentration more accurately and predict long-term exposure, thus informing future epidemiological studies. Since no biomarkers of effect specific to DEHP exposure have been identified, studies identifying biomarkers specific to DEHP effects would fill a data gap.

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetic properties of DEHP are well characterized for oral exposure. Data on the toxicokinetic properties of DEHP following inhalation

and dermal exposure are limited to dermal absorption (Chu et al. 1996; Deisinger et al. 1998; Elsisi et al. 1989; Wester et al. 1998) and general metabolism (Albro 1986; Choi et al. 2012; Hopf et al. 2014); therefore, additional toxicokinetic data for these exposure routes would be useful.

Comparative Toxicokinetics. The optimization and validation of available PBPK models (Adachi et al. 2015; Keys et al. 1999) against observations in humans could provide valuable information in extrapolating animal toxicity data to humans.

Children's Susceptibility. Available data are not adequate to evaluate whether children are more susceptible to the hepatic or renal effects of DEHP; additional studies would fill this data gap.

Physical and Chemical Properties. Most of the physical and chemical properties of DEHP are sufficiently well characterized to allow estimation of its environmental fate and transport profile. On this basis, it does not appear that further research in this area is required. However, the experimental and theoretical water solubility values for DEHP differ by several orders of magnitude (1.1–1,200 µg/L). Additional experimental data are needed to decrease uncertainty in this value, particularly experiments using the slow-stir method.

Production, Import/Export, Use, Release, and Disposal. Data on the production and uses of DEHP in the United States are available (CPSC 2010a; TRI18 2020). Production is dependent on the PVC markets. Disposal of DEHP is mainly to landfills, and land disposal restrictions should ensure reduction of the disposal of untreated DEHP wastes. Available information appears to be sufficient for assessing the potential for release of, and exposure to, DEHP.

While information on uses is available (CPSC 2010a), specific information on uses in certain potentially high-exposure applications is either changing or lacking. For example, even though toy manufacturers have discontinued use of phthalates in certain products and Congress limited the content of DEHP in children's toys and child care articles (CPSIA 2008), DEHP use and exposure levels from other products are currently not known. Specifically, information on the use of DEHP as an indirect additive in food contact applications such as coatings used in cans, bottle caps, and films would allow a better estimation of potential exposures from food. Currently, the only information available is that indirect applications are allowed by FDA rules (FDA 1999a, 1999b, 1999c, 1999d, 1999e, 1999f, 1999g), but it is unclear if DEHP is used.

Environmental Fate. The environmental fate of DEHP has been fairly well characterized. As described in Section 5.4, its transport in the atmosphere, sorption to sediments, bioconcentration in aquatic organisms, and biodegradation by water and soil microorganisms seem to be well understood. Sorption and biodegradation are competing processes for DEHP removal from water (Ritsema et al. 1989; Wams 1987). The half-life for the reaction of vapor-phase atmospheric DEHP with photochemically generated hydroxyl radicals is about 6 hours when estimated using the Atmospheric Oxidation Program (AOP) (Meylan and Howard 1993). However, adsorption to aerosols or particulate matter in the atmosphere may attenuate photodegradation since atmospheric oxidants, such as hydroxyl radicals, react slowly with chemicals in the particulate phase. Additional data on photodegradation of particulate-phase DEHP would be useful for more accurately predicting the fate of DEHP in the atmosphere. Of interest would be additional information on the fate of DEHP leached into groundwater in order to document further that it is of minor concern in subsurface environments. In designing such studies, it is critical to address the issue of laboratory contamination by the DEHP contained in some labware.

Bioavailability from Environmental Media. On the basis of data from available toxicokinetics studies, DEHP will be absorbed following ingestion of contaminated drinking water and foodstuffs and inhalation of contaminated ambient air. Absorption following dermal exposure to soils is expected to be limited because of the strong sorption of DEHP to soils and because, in the absence of solvents, DEHP does not penetrate skin well. However, additional information would be useful to determine whether DEHP would be absorbed following dermal exposure to contaminated water or after ingesting contaminated soils. This information will be helpful in assessing the relative importance of these pathways for exposed humans.

Food Chain Bioaccumulation. Bioconcentration of DEHP in aquatic organisms has been documented for several aquatic species (Barrows et al. 1980; EPA 1980; Kenaga 1980; Staples et al. 1997). Based on the relatively high K_{ow}, it appears that accumulation can occur. However, rapid metabolism of DEHP in higher organisms seems to prevent biomagnification in the food chain (EPA 1979; Johnson et al. 1977; Staples et al. 1997; Wofford et al. 1981).

Exposure Levels in Environmental Media. Several studies are available documenting levels of DEHP in air, water, sediments, and biota in rural and urban areas during the 1980s and 1990s. DEHP has been detected in surface water, groundwater, and soil samples taken in the environs of hazardous waste sites during monitoring surveys (Canter and Sabatini 1994; Eckel et al. 1993; Hauser and Bromberg 1982; Plumb 1987). Concentrations in ambient air at hazardous waste sites are available at only four sites.

Ambient levels of DEHP are generally low in all environmental media. Since DEHP is a ubiquitous laboratory contaminant, it is very difficult to accurately determine these low levels. Often, laboratory contamination has undermined the credibility of the data generated. More recent monitoring data for DEHP in all environmental media, using recently suggested techniques for reducing laboratory contamination, would be useful to better assess the potential for human exposure to this compound.

Exposure Levels in Humans. Detectable levels of DEHP in blood, urine, and adipose tissue are indicators of human exposure. Additional data correlating levels in environmental media and consumer products with human tissue levels of DEHP or its metabolites would be helpful in establishing levels of DEHP to which humans have been exposed.

Exposures of Children. Although much is known about historical exposure of children to DEHP, little is known about current exposure levels in children since the chemical has been withdrawn from many uses and products. DEHP is widely used in many applications that can result in exposures. Toys were once considered an important route of exposure for children, especially in children <36 months of age, but willing phase out and a Congressional ban on DEHP in toys, teethers, and pacifiers has changed this from an important route. However, there is only limited information on children's DEHP exposures from items commonly encountered within the household and elsewhere (e.g., automobile interiors, daycare centers, schools, hospitals, playgrounds, etc.). In addition, more information on exposure to dust containing DEHP in the United States would be useful, since ingestion of such dust might be a significant source of exposure for children. This type of information along with indoor vapor measurements would allow a more accurate estimation of indoor exposures where children, and especially young children, spend significant amounts of time. Given current restrictions in the United States, exposure assessment may require revisiting with greater emphasis on medical exposures in childcare or treatment.

6.3 Ongoing Studies

There are numerous ongoing studies evaluating the potential adverse effects of DEHP exposure in humans and laboratory animals, as well as underlying mechanisms of toxicity (Table 6-1). Most ongoing studies are focused on developmental and reproductive toxicity endpoints.

Table 6-1. Ongoing Studies on DEHP

Investigator	Affiliation	Research description	Sponsor
Human studies			
Vaia Lida Chatzi	University of Southern California	Developmental origins of child liver injury: effects of prenatal environmental exposure	NIEHS
Catherine J. Karr	University of Washington	Prenatal and early childhood pathways to health: an integrated model of chemical and social exposures, biological mechanisms, and sex-specific effects on neurodevelopment and respiratory outcomes	Office of the Director, NIH
Eva Laura Siegel	Columbia University Health Sciences	Strengthening policy-relevant evidence in environmental epidemiology: dose-response curve estimation for varying exposure distributions	NIEHS
Leonardo Trasande	New York University School of Medicine	Preconceptual bisphenol and phthalate effects on early embryonic development	NIEHS
Leonardo Trasande	New York University School of Medicine	New York University pediatric obesity, metabolism, and kidney cohort center	Office of the Director, NIH
Lauren A. Wise	Boston University Medical Campus	A preconception cohort study of environmental chemicals, fertility, and miscarriage	NIEHS
Animal toxicity studies (some with associated mechanistic studies)			
Marisa S. Bartolomei	University of Pennsylvania	Preconception phthalate exposure and offspring outcomes	NIEHS
Zelieann Rivera Craig	University of Arizona	Environmentally relevant phthalate exposures and ovarian function	NIEHS
Jodi A. Flaws	University of Illinois at Urbana-Champaign	Phthalates and ovarian toxicity	NIEHS
Daniel James Spade	Brown University	Retinoic acid signaling disruption by phthalates in human and rodent fetal testis	NIEHS
Mechanistic studies			
Dana Dolinoy	University of Michigan	Perinatal exposures, tissue- and cell-specific epigenomics, and lifecourse outcomes	NIEHS
Rita K. Loch-Caruso	Northeastern University	Toxicant-Stimulated Disruption of Gestational Tissues with Implications for Adverse Pregnancy Outcomes	NIEHS
Ayana Henderson	Harvard medical School	Assessing the effects of exposures to phthalates in both the female and male germlines	NIEHS
Richard J. Pilsner	University of Massachusetts Amherst	Male preconception phthalates and offspring embryo and sperm allele-specific methylome programming	NIEHS
John H. Richburg	University of Texas, Austin	Sertoli cell toxicant injury and mechanisms of testicular germ cell apoptosis	NIEHS
Alicia R. Timme-Laragy	University of Massachusetts Amherst	Activation of NRF2 during embryonic development: mechanisms and consequences	NIEHS

Table 6-1. Ongoing Studies on DEHP

Investigator	Affiliation	Research description	Sponsor
Kassim Traore	Campbell University	*In vitro* analysis of the effects of acute and chronic phthalate exposures on Leydig cell testosterone production, and the molecular mechanisms involved	NIEHS
Toxicokinetics/biomarkers			
Ock K. Chun	University of Connecticut Storrs	Assessment of risk of exposure to estrogenic chemicals via capsule coffee consumption	NIEHS

DNA = deoxyribonucleic acid; NIEHS = National Institute of Environmental Health Sciences; NIH = National Institutes of Health; NRF2= nuclear factor erythroid 2-related factor

Source: RePORTER 2021